LISATA THERAPEUTICS, INC.

CLINICAL STUDY PROTOCOL

PHASE 2a

Full Title: A Phase 2a, double-blind, placebo-controlled, multi-center, randomized study evaluating LSTA1 when added to standard of care (SoC) versus standard of care alone in subjects with advanced solid tumors (BOLSTER)

Short Title: LSTA1 Phase 2a basket trial in advanced solid tumors

PROTOCOL NUMBER: LSTA1-P02

ClinicalTrials.gov Identifier: NCT05712356
EU CT Number: 2023-503740-14-00
Universal Trial Number: U1111-1291-8700

Version Number: 8.0

Version Date: 16 July 2024

Study Sponsor: Lisata Therapeutics, Inc.
110 Allen Road, Second Floor
Basking Ridge, NJ 07920
United States

CONFIDENTIALITY STATEMENT

PROTOCOL APPROVAL FORM

CLINICAL STUDY PROTOCOL

LSTA1-P02

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APPROVAL SIGNATURES:

[redacted]

INVESTIGATOR ACKNOWLEDGEMENT

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By signing below, the investigator acknowledges that he/she has read and understands this protocol and provides assurance that this study will be conducted according to all requirements as defined in this protocol, the clinical study agreement, International Council on Harmonisation Good Clinical Practice guidelines, and all applicable regulatory requirements.

Investigator Signature Date

Print Name and Title of Investigator

PERSONNEL AND FACILITIES

Sponsor Lisata Therapeutics, Inc. 110 Allen Road, Second Floor Basking Ridge, NJ 07920 USA Main: (908) 842-0100	**Contact for Reporting Serious Adverse Events** [redacted]
Medical Monitor [redacted]	**Study Manager (Primary Study Contact)** [redacted]

Note: Changes to Personnel and Facilities do not constitute an amendment and will be updated as needed.

PROTOCOL VERSION 8.0 SUMMARY OF KEY CHANGES

The following sections have been amended:

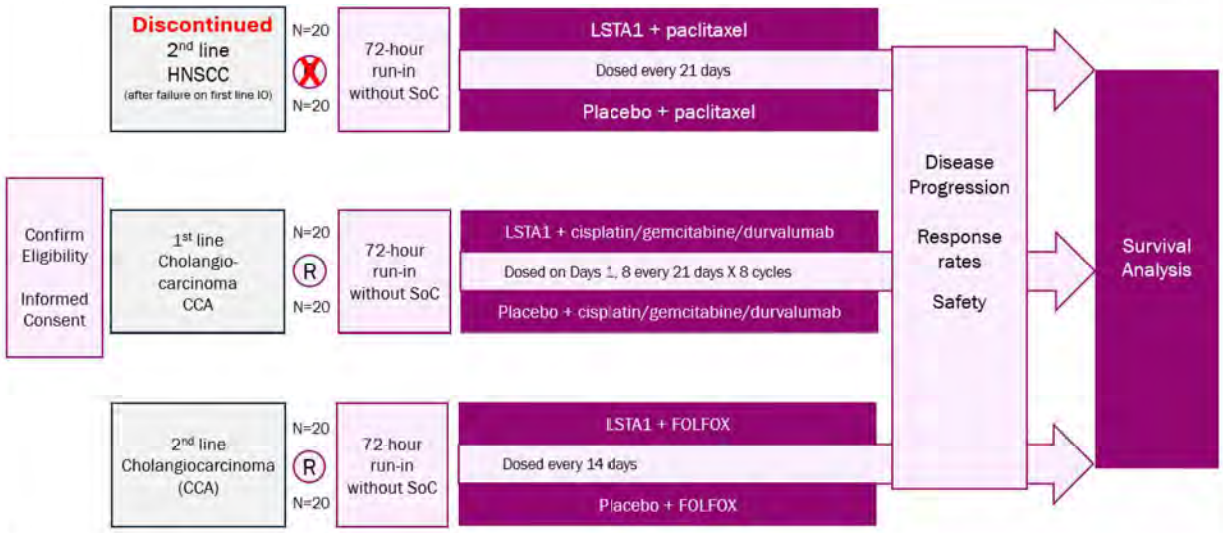
Description of Change	Applicable Sections
Change of the leucovorin dose to match the most common standard of care amongst trial investigators	Throughout protocol
Clarification that tumor assessments are not required after the end of study visit	Schedule of Assessments
Update to the allowable FOLFOX dose modification to allow for dropping the 5-FU bolus in the event of repeated grade 3 drops in neutrophil counts	Section 11.9.2.3

In addition to the changes above, the LSTA1-P02 protocol may have been edited for style, formatting, clarity, and consistency.

1. STUDY SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	LSTA1 (previously known as CEND-1)
CLINICAL CONDITION(S)/INDICATION(S)	
Advanced head and neck squamous cell carcinoma and cholangiocarcinoma	
PROTOCOL ID	LSTA1-P02
PROTOCOL TITLE	A Phase 2a, double-blind, placebo-controlled, multi-center, randomized study evaluating LSTA1 when added to standard of care (SoC) versus standard of care alone in subjects with advanced solid tumors (BOLSTER)
Short Title	LSTA1 Phase 2a basket trial in advanced solid tumors
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
To investigate the safety, tolerability, and preliminary efficacy of LSTA1 in combination with standards of care in subjects with advanced solid tumors	
STUDY DESIGN	
Study Type	Interventional
Control Type	Placebo-controlled in combination with standard of care
Blinding Schema	Double-blind
Study Design	This is a Phase 2a, double-blind, placebo-controlled, multi-center, randomized study of LSTA1 when added to SoC versus SoC alone in subjects with advanced solid tumors. The study will consist of a screening period, a run-in period, a treatment period, an end-of-treatment follow-up visit, and a long-term follow up period. Survival and subsequent anti-cancer therapies will be assessed during the long-term follow-up. The study includes subjects with advanced head and neck squamous cell carcinoma and cholangiocarcinoma. However, the enrollment of the cohort for advanced head and neck squamous cell carcinoma was discontinued after only 3 subjects were randomized and treated due to a slower than anticipated enrollment rate.

Study Schema:



Screening Period:	Subjects who provide informed consent will be screened for eligibility within 28 days prior to beginning the study treatment run-in period. Subjects must meet all inclusion criteria and none of the exclusion criteria to be eligible for this trial. Screening information for eligible subjects, including clinical evaluation, laboratory assessments, tumor biomarkers, imaging, collection of archival tumor tissue if available, and pregnancy test should be recorded in the electronic Case Report Form (eCRF).
Randomization and Run-In:	Once eligibility is confirmed, subjects will be *randomized within their respective tumor type basket arm* 1:1 to one of the two treatment groups (i.e., SoC + placebo vs. SoC + LSTA1). During the 72-hour run-in, subjects will only receive the LSTA1 or placebo components of their randomized treatment regimen; they will not receive SoC chemotherapy. On Day 1 of the run-in, subjects will either be given LSTA1 or matching placebo as a slow intravenous push over one minute (± 30 seconds).
Treatment Period:	After the 72-hour run-in, Cycle 1 of treatment will commence. Tumor assessments will be performed every 8 weeks (56 days ± 7 days) from Cycle 1 Day 1 (C1D1) until disease progression or a new anti-cancer therapy is commenced. Tumor assessments will occur at this interval for up to 12 months and then be performed every 12 weeks (± 7 days) thereafter until treatment is discontinued. Imaging for screening and tumor assessments must be performed using the same imaging modality as the baseline scans. Those who do not progress will

	continue to have scans for up to 12 months after the last patient is enrolled. Laboratory evaluations will be performed prior to treatment initiation and on treatment days. Dose modifications/reductions of SoC chemotherapies are allowable to manage toxicities. Every effort should be made to provide maximal supportive therapy prior to implementing a dose reduction. The dose of LSTA1/matching LSTA1 placebo will not be adjusted.
Investigational Product Administration:	**Advanced Head and Neck Squamous Cell Carcinoma:** Subjects with advanced head and neck squamous cell carcinoma who have progressed on 1L immunotherapy will be randomly assigned 1:1 to one of two treatment arms: Treatment Group 1: • LSTA1 3.2 mg/kg in combination with paclitaxel 175 mg/m^2 IV every 21 days Treatment Group 2: • Matching LSTA1 placebo in combination with paclitaxel 175 mg/m^2 IV every 21 days **First-line (1L) Cholangiocarcinoma:** Subjects with previously untreated, advanced (unresectable), or metastatic cholangiocarcinoma will be randomly assigned (1:1) to one of two treatment arms: Treatment Arm 1: • LSTA1 3.2 mg/kg in combination with 1500 mg of durvalumab IV, cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 1, and LSTA1 3.2 mg/kg in combination with cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 8 - every 21 days up to 8 cycles. After 8 cycles, LSTA1 3.2 mg/kg will be given in combination with 1500 mg of durvalumab IV as monotherapy every 28 days. Treatment Arm 2: • Matching LSTA1 placebo in combination with 1500 mg of durvalumab IV, cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 1, and matching LSTA1 placebo in combination with cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 8 - every 21

	days up to 8 cycles. After 8 cycles, matching LSTA1 placebo will be given in combination with 1500 mg of durvalumab IV as monotherapy every 28 days. **Second line (2L) Cholangiocarcinoma:** Subjects with metastatic or unresectable cholangiocarcinoma with clear evidence of progression of disease after 1L chemotherapy with gemcitabine and immunotherapy (i.e., PD-1/PD-L1 monoclonal antibody treatment) will be randomly assigned (1:1) to one of two treatment arms: <u>Treatment Group 1:</u> • LSTA1 3.2 mg/kg in combination with oxaliplatin 85 mg/m² IV, l-folinic acid 200 mg/m² **or** d,l-folinic acid 400 mg/m² IV, and fluorouracil (5-FU) 400 mg/m² (IV bolus) on day 1 followed by a continuous 46-hour infusion of 5-FU 2400 mg/m² repeated every 14 days <u>Treatment Group 2:</u> • Matching LSTA1 placebo in combination with oxaliplatin 85 mg/m² IV, l-folinic acid 200 mg/m² **or** d,l-folinic acid 400 mg/m² IV, and fluorouracil (5-FU) 400 mg/m² (IV bolus) on day 1 followed by a continuous 46-hour infusion of 5-FU 2400 mg/m² repeated every 14 days
<u>Sequence of Administration After Run-In:</u>	**Head and Neck Squamous Cell Carcinoma:** **Day 1:** • Paclitaxel 175 mg/m² will be administered over 3 hours (± 30 minutes) followed by a saline flush of the IV line. • Immediately (within 15 minutes) following paclitaxel administration, LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be given as a slow IV push over 1 minute (± 30 seconds). **1L Cholangiocarcinoma: First 8 cycles; every 21 days** **Day 1:** • Durvalumab will be administered first as an intravenous infusion for 60 minutes (± 10 minutes). It should be administered via an intravenous line according to the United States Product Insert (USPI) or relevant local dosing instructions.*

* IMFINZI-durvalumab injection, solution. AstraZeneca Pharmaceuticals. U.S. prescribing information. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8baba4ea-2855-42fa-9bd9-5a7548d4cec3

	• Cisplatin 25 mg/m^2 IV will then be administered over 30 to 65 minutes followed by a saline flush of the IV line. • Immediately (within 15 minutes) following cisplatin administration, LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be given as a slow IV push over 1 minute (± 30 seconds). • Gemcitabine 1000 mg/m^2 will be administered over 30 minutes (± 5 minutes) starting no more than 10 minutes after the completion of LSTA1 administration **Day 8:** • Cisplatin 25 mg/m^2 IV will then be administered over 30 to 65 minutes followed by a saline flush of the IV line. • Immediately (within 15 minutes) following cisplatin administration, LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be given as a slow IV push over 1 minute (± 30 seconds). • Gemcitabine 1000 mg/m^2 will be administered over 30 minutes (± 5 minutes) starting no more than 10 minutes after the completion of LSTA1 administration **1L Cholangiocarcinoma: After cycle 8; every 28 days** **Day 1:** • Durvalumab will be administered first as an intravenous infusion for 60 minutes (± 10 minutes). It should be administered via an intravenous line according to the USPI or relevant local dosing instructions.[†] • Immediately (within 15 minutes) following durvalumab administration, LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be given as a slow IV push over 1 minute (± 30 seconds). **2L Cholangiocarcinoma: every 14 days** **Day 1:** • Oxaliplatin 85 mg/m² and l-folinic acid 200 mg/m^2 **or** d,l-folinic acid 400 mg/m^2 will be administered first, concurrently, as a 2-hour (± 15 minutes) intravenous infusion.

[†] IMFINZI-durvalumab injection, solution. AstraZeneca Pharmaceuticals. U.S. prescribing information. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8baba4ea-2855-42fa-9bd9-5a7548d4cec3

	• Immediately (within 10 minutes) following the oxaliplatin and folinic acid infusion, fluorouracil (5-FU) 400 mg/m² will be given as an intravenous bolus over 5 minutes (± 5 minutes). • Following the 5-FU bolus (within 10 minutes), LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be administered as a slow IV push over 1 minute (± 30 seconds). • Upon completion of the LSTA1 IV push or matching LSTA1 placebo (within 10 minutes), a continuous infusion (via home-infusion pump) of 5-FU 2400 mg/m² will be administered over 46 hours
Planned Sample Size	At least 40 subjects are planned for each cholangiocarcinoma cohort (~N=20/arm). Enrollment in the HNSCC cohort was discontinued after 3 subjects were randomized and treated due to an unanticipated slow enrollment rate. The expected total sample size is approximately ~83 subjects.
Study Duration	Approximately 36 months
Outcome Measures	
Safety Objectives	**Corresponding Endpoints**
• To evaluate the safety of LSTA1 in combination with SoC therapies compared to SoC therapies alone	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v. 5.0 • Frequency of Grade ≥ 3 treatment-related adverse events • Frequency of treatment-related serious adverse events (SAEs) • Electrocardiograms • Clinical laboratory investigations • Physical examinations • Vital signs
• To evaluate the impact on dose of SoC when administered in combination with LSTA1	• Mean SoC drug dose delivered per cycle • Mean dose of SoC over 3 cycles and over 6 cycles • Mean number of dose modifications (i.e., dose reductions, interruptions, and discontinuations per cycle (up to first 6 cycles)

• To assess the baseline safety of LSTA1 monotherapy when administered during 72-hour run-in period to patients with advanced solid tumors	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v. 5.0 • Frequency of Grade ≥ 3 treatment-related adverse events • Frequency of treatment-related SAEs
Efficacy Objectives	**Corresponding Endpoints**
• To determine the effect of LSTA1 in combination with SoC chemotherapy on survival relative to placebo in combination with SoC in patients with advanced solid tumors	• Median time from randomization until death due to any cause
• To determine the effect of LSTA1 on milestone survival endpoints	• 3-month survival • 6-month survival • 12-month survival
• To determine the effect of LSTA1 on PFS	• Median progression-free survival (PFS) based on RECIST 1.1 [Time Frame: From first dose until objective radiological progression, or death from any cause, whichever comes earlier, assessed until the data cut-off is reached.]
• To determine the effect of LSTA1 on response rate	• Objective response rate (ORR) [Complete response (CR) + Partial response (PR)] based on RECIST 1.1. ORR is relative to the screening tumor measurement. • Disease control rate (DCR) [CR + PR + Stable disease (SD) lasting > 16 weeks (CR+PR+SD for > 16 weeks) based on RECIST 1.1].
• To determine the effect of LSTA1 on duration of response (DOR) in responding patients with measurable disease at baseline	• Duration of response (DOR) for responding patients with measurable disease at baseline, which is measured from the first timepoint where an objective response is determined until the last timepoint the patient is found to have an objective response.
Pharmacodynamic Objective	**Corresponding Endpoints**
• To evaluate the pharmacodynamic profile of LSTA1 when administered in combination with SoC therapies	• Retrospective assessment of tissue biomarkers in optional pre-treatment archival tissue (or pre-treatment core

	biopsy) and on-treatment optional core biopsy. • Assessment of baseline and on treatment serum biomarkers
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the Pharmacokinetic (PK) profile of LSTA1 when administered in combination with SoC therapies • To characterize the population PK profile of LSTA1 when administered in combination with SoC therapies	• PK of LSTA1 via: ○ Half life ○ T_{max} ○ C_{max} ○ AUC_{0-t} ○ $AUC_{0-\infty}$ • Other PK parameters as described in the SAP (or PK analysis plan, if separate).
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Investigational (Active) Product	**Dosage form**: LSTA1 Solution **Dose:** 3.2 mg/kg LSTA1 by intravenous injection **Mode of Administration:** Slow intravenous push over one minute (± 30 seconds)
SUBJECT SELECTION	
Planned # of Subjects	~83 (at least 40 for each cholangiocarcinoma cohort and 3 for the HNSCC cohort)
Population to be Studied	Men and women ≥ 18 years of age with advanced solid tumors (head and neck squamous cell carcinoma and cholangiocarcinoma)

Inclusion Criteria All Subjects

1. Subjects must be ≥ 18 years of age at time of consent and provide informed consent
2. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
3. Life expectancy ≥ 3 months, as determined by the investigator
4. At least one bidimensional measurable target lesion assessed by RECIST 1.1. Tumor lesion located in the area of previous radiotherapy or other local and regional treatment sites is generally not a measurable lesion unless there is definite progression of the lesion, or the lesion persists three months after radiotherapy. Additionally, a biopsy site should not be considered a target lesion.
5. Adequate organ and marrow function:
    - Platelets ≥ 100 x 10^9/L (>100,000 per mm^3)
    - WBC ≥ 3000/µL
    - Absolute neutrophil count ≥ 1.5 x 10^9/L
    - Serum albumin ≥ 2.5 g/L
    - ALT and AST ≤ 2.5 x ULN in the absence of liver metastases or < 5 x ULN in the presence of liver metastases

- Bilirubin ≤ 1.5 x ULN
- Hemoglobin ≥ 9.0 g/dL. Labs may be drawn 24 hours after a transfusion to meet this criterion.
- INR < 1.5 (for patients not receiving therapeutic anticoagulation)
- Adequate respiratory and cardiac function (PaO_2 ≥ 60 mm Hg or oxygen saturation ≥ 92% on room air, and 12-lead ECG with normal tracing or non-clinically significant changes that do not require medical intervention)
- QT interval corrected using the Fridericia method (QTcF) < 470 ms

6. Adequate contraception:

    - All female patients will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically. Female patients of childbearing potential must agree to use two forms of highly effective contraception methods (a primary and a secondary method – see next bullet) during the study and for a period of 6 months following the last administration of the study drug, unless subject received cisplatin whereby aforementioned contraception methods must be adhered to for 14 months.
    - Male patients and their female partners, who are of childbearing potential and are not practicing total abstinence, must agree to use two forms of highly effective contraception methods (a primary and a secondary method) during the study and for a period of 6 months following the last administration of the study drug, unless subject received cisplatin whereby the following contraception methods must be adhered to for 14 months. These contraception methods include oral, transdermal, systemic or implant contraception birth control, intra-uterine devices (IUD), abstinence and double barrier method such as diaphragm with spermicidal gel or other recommended double barrier methods screening.

Inclusion Criteria 2L Head and Neck Squamous Cell Carcinoma (HNSCC):

7. Patients with histologically confirmed recurrent or metastatic HNSCC that is unresectable or considered incurable by local therapies and that has progressed after 1L immunotherapy

    - Characterization of tumor PD-L1 expression using the PD-L1 IHC 22C3 PharmDx Assay
    - Receipt of prior treatment with checkpoint inhibitors as a single agent and have received at least 2 doses of the agent or a minimum of 6 weeks on treatment
    - Have documented clinical or radiographic progression by RECIST 1.1

8. The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx. Patients may not have primary tumor sites of the skin, paranasal sinuses, or the nasopharynx (any histology).‡

Inclusion Criteria 1L Cholangiocarcinoma:

11. Pathologically confirmed metastatic or unresectable cholangiocarcinoma or gallbladder carcinoma (GBC), with no prior systemic chemotherapy or targeted therapy or loco-regional therapy (including but not limited to transarterial chemoembolization, transarterial embolization, transarterial chemotherapy or transarterial radioembolization). Patients with recurrent disease more than 6 months after completion of adjuvant chemotherapy following curative resection are eligible.
    a) Includes intrahepatic cholangiocarcinoma (IHC), extrahepatic cholangiocarcinoma (EHC), and GBC, but not ampulla of Vater cancers
    b) For liver dominant IHC, disease must comprise < 60% of the liver parenchyma, as defined by the investigator
12. If the patient has had decompression of the biliary tree within the last 14 days, stability of the bilirubin level needs to be confirmed with two measurements that are within 5 to 7 days of each other; (the second measurement must be obtained within 7 days prior to randomization); both the first and second measurement must be ≤ 1.5 x ULN; stability is defined as the second measurement being no more than one point higher than the first measurement

Inclusion Criteria 2L Cholangiocarcinoma

13. Pathologically confirmed metastatic or unresectable cholangiocarcinoma or GBC
    a) Includes intrahepatic cholangiocarcinoma (IHC), extrahepatic cholangiocarcinoma (EHC), and GBC, but not ampulla of Vater cancers
    b) For liver dominant IHC, disease must comprise < 60% of the liver parenchyma, as defined by the investigator
14. Clear evidence of progression of disease ***after*** 1L chemotherapy with gemcitabine and immunotherapy (i.e., PD-1/PD-L1 monoclonal antibody treatment), gemcitabine, cisplatin and immunotherapy, or immunotherapy +/- gemcitabine maintenance therapy. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are eligible. If a patient received adjuvant treatment and had disease recurrence after 6 months, they will only be eligible after experiencing disease progression on one line of chemotherapy used to treat the disease recurrence.
15. If the patient has had decompression of the biliary tree within the last 14 days, stability of the bilirubin level needs to be confirmed with two measurements that are within 5 to 7 days of each other; (the second measurement must be obtained within 7 days prior to randomization); both the first and second measurement must be ≤ 1.5

‡ Inclusion criteria 9 and 10 were removed beginning with version 6 of the protocol.

x ULN; stability is defined as the second measurement being no more than one point higher than the first measurement

Exclusion Criteria for All Subjects:

1. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results, including but not limited to:
    - Any major surgery or irradiation less than 4 weeks prior to baseline disease assessment
    - Active infection (viral, fungal, or bacterial) requiring systemic therapy
    - Known active hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) infection
    - Active tuberculosis as defined per local guidance
    - History of allogeneic tissue/solid organ transplant
    - Prior malignancy requiring active treatment within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast
    - Pregnant or breastfeeding
    - Clinically significant or symptomatic cardiovascular/cerebrovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before randomization
2. Subjects with a known sensitivity to LSTA1 or its excipients
3. Patients with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent
4. Have received chemotherapy, radiotherapy, biotherapy, endocrine therapy, immunotherapy, and other anti-tumor therapy within 28 days prior to randomization **(not applicable to 2L CCA)**
5. History or clinical evidence of central nervous system (CNS) metastases; exceptions include:
    - Subjects who have completed local therapy and who meet both of the following criteria:
        - Subjects must be asymptomatic AND
        - Subjects must have no requirement for steroids 6 weeks prior to start of study treatment. Screening with CNS imaging [CT or magnetic resonance imaging (MRI)] is required only if clinically indicated or if the subject has a history of CNS metastases

Exclusion Criteria 2L Head and Neck Squamous Cell Carcinoma (HNSCC):

6. Patients who received prior taxanes unless it was given as part of neoadjuvant, concurrent therapy in the curative intent setting, and it has been more than 6 months since last dose
7. Known allergies to taxanes or their standard pre-treatments
8. Any surgery involving the HNSCC for which the patient is being treated (except biopsies) that occurred within 28 days prior to randomization
9. Subjects who cannot discontinue any concomitant medications that are inducers or inhibitors of CYP2C8 (e.g., rifampicin, phenobarbital, secobarbital, phenytoin, clopidogrel, gemfibrozil, zafirlukast, felodipine) or CYP3A4 (e.g., dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin/rifampicin, rifabutin, St. John's Wort, erythromycin, itraconazole, ritonavir, verapamil) during treatment with paclitaxel
10. Creatinine clearance < 45 mL/min (calculated using the Cockcroft-Gault formula below)
    - Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL
    - Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL[§]

Exclusion Criteria 1L Cholangiocarcinoma:

16. Patients who received prior palliative systemic treatment for their advanced cancer
17. Patients with a history of idiopathic pulmonary fibrosis (pneumonitis requiring treatment with steroids), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on baseline imaging
18. Patients with a history of active interstitial lung disease
19. Concurrent use of immunosuppressive medication, EXCEPT for the following:
    a. Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection)
    b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

[§] Exclusion criteria 11 through 15 were removed beginning with version 6 of the protocol.

20. Active autoimmune disease that might deteriorate when receiving an immune-stimulatory agent. Patients with Type 1 diabetes, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.
21. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)
22. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab. Note: While enrolled, patients should not receive any live vaccines while receiving durvalumab and up to 30 days after last dose of durvalumab.
23. Patients who experience any grade 3-4 gastrointestinal (GI) bleeding within 3 months preceding randomization
24. Diagnosis of sclerosing cholangitis
25. Diagnosis of hepatic encephalopathy
26. Current biliary obstruction requiring surgical diversion or placement of endoscopic or transhepatic stents for biliary decompression
27. Clinically significant ascites (palpable on exam, paracentesis within 3 months preceding randomization, and/or symptomatic)
28. History of malignant bowel obstruction
29. Subjects with creatinine clearance < 60 mL/min (calculated using the Cockcroft-Gault formula below)
    - Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL
    - Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL

Exclusion Criteria 2L Cholangiocarcinoma:

30. In the opinion of the investigator, subject has had an Incomplete recovery from previous therapy(ies)
31. Concurrent use of immunosuppressive medication, EXCEPT for the following:
    a) Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection)
    b) Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent
    c) Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
32. Patients who experience any grade 3-4 GI bleeding within 3 months preceding randomization

33. Diagnosis of sclerosing cholangitis
34. Diagnosis of hepatic encephalopathy
35. Current biliary obstruction requiring surgical diversion or placement of endoscopic or transhepatic stents for biliary decompression
36. Clinically significant ascites (palpable on exam, paracentesis within 3 months preceding randomization, and/or symptomatic)
37. History of malignant bowel obstruction
38. Subjects with creatinine clearance < 60 mL/min (calculated using the Cockcroft-Gault formula below)
    - Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL
    - Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL

STATISTICAL CONSIDERATIONS

Planned Statistical Analyses

Formal sample size calculations were not performed for this Phase 2a, placebo-controlled, proof-of-concept basket trial.

Descriptive statistical methods will be used to summarize the efficacy, safety, and PK data from this study, with hypothesis testing performed for the primary and other selected efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum and maximum for continuous data and frequencies and percentages for categorical data.

Efficacy analysis methods may include Kaplan-Meier survival analysis, analysis of covariance (ANCOVA), and Cox regression, mixed models, or logistic regression. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number.

The term 'treatment group' refers to all subjects in a specific tumor type basket arm dosing regimen.

There will be two (2) treatment groups in each cohort of this study:

HNSCC[**]

- LSTA1 3.2 mg/kg in combination with paclitaxel 175 mg/m^2 IV
- Matching LSTA1 placebo in combination with paclitaxel 175 mg/m^2 IV

[**] The HNSCC cohort was terminated early. Data for subjects in the HNSCC cohort will be included in the data listings and safety tables. No efficacy tables will be prepared for the HNSCC cohort.

1L Cholangiocarcinoma

- LSTA1 3.2 mg/kg in combination with 1500 mg of durvalumab IV, cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 1, and LSTA1 3.2 mg/kg in combination with cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 8; every 21 days for 8 cycles followed by LSTA1 3.2 mg/kg in combination with 1500 mg of durvalumab IV as monotherapy every 28 days
- Matching LSTA1 placebo in combination with 1500 mg of durvalumab IV, cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 1, and matching LSTA1 placebo in combination with cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 8; every 21 days for 8 cycles followed by matching LSTA1 placebo in combination with 1500 mg of durvalumab IV as monotherapy every 28 days

2L Cholangiocarcinoma

- LSTA1 3.2 mg/kg in combination with oxaliplatin 85 mg/m² IV, l-folinic acid 200 mg/m^2 **or** d,l-folinic acid 400 mg/m^2 IV, and fluorouracil (5-FU) 400 mg/m² (IV bolus) on day 1 followed by a continuous 46-hour infusion of 5-FU 2400 mg/m² repeated every 14 days

Matching LSTA1 placebo in combination with oxaliplatin 85 mg/m² IV, l-folinic acid 200 mg/m^2 or d,l-folinic acid 400 mg/m^2 IV, and fluorouracil (5-FU) 400 mg/m² (IV bolus) on day 1 followed by a continuous 46-hour infusion of 5-FU 2400 mg/m² repeated every 14 days Any statistical tests performed will be two-sided with an alpha level of 0.05. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

Safety Analysis:

All patients who receive any amount of study drug will be included in the final summaries and listings of safety data.

Frequencies of patients experiencing at least one adverse event (AE) will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Intensity (severity) of the AEs will be graded according to the CTCAE v5.0.

Summary tables will present the number of patients observed with AEs and corresponding percentages. The denominator used to calculate incidence percentages consists of patients receiving at least one dose of study drug. Within each table, the AEs will be categorized by MedDRA body system and preferred term. Additional subcategories will be based on event intensity and relationship to study drug.

Deaths and other SAEs will be tabulated.

Vital signs will be summarized using descriptive statistics.

Summary tables will be prepared to examine the distribution of laboratory measures over time.

Pharmacokinetic Analysis:

Concentration-time profiles will be constructed from the plasma samples obtained. Estimates of the area under the concentration versus time curve (AUC) and slope of the terminal decay phase will be used to calculate values of the following PK parameters: apparent terminal phase half-life ($t_{1/2}$), total body clearance (CL), apparent time of maximum concentration (T_{max}), and apparent volume of distribution (Vd). The plasma profiles will also be fitted by nonlinear regression analysis whenever possible.

A population PK analysis of data combined from multiple trials will also be performed.

Pharmacodynamic Analysis:

Pharmacodynamic analyses will be summarized using descriptive statistics, if applicable.

Subject Disposition, Demographic, and Baseline Characteristics

Subject disposition will be presented for all randomized subjects. For each treatment group the following will be presented: the number of subjects who meet all eligibility criteria, the number of subjects included in each analysis set, the number of subjects who completed the study and discontinued from the study, and the reasons for early discontinuation at any point. The number of subjects dosed will be presented and the number of days on study treatment will be summarized for all treated subjects. The number of dose interruptions, modifications, and discontinuations of all anti-cancer medication discontinuations will be summarized.

Demographic data and baseline characteristics including age, sex, race, and ethnicity, weight at Baseline, height at Baseline, and labs will be summarized using descriptive statistics for the Safety population and will be presented by treatment group. This information will be reviewed for baseline differences, but no statistical testing will be performed.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an AE that occurs during or after initiation of study drug. The number and percentage of subjects with TEAEs will be summarized by MedDRA System Organ Class and Preferred Term overall, by severity and by relationship to study drug or procedures.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	First-line
2L	Second-line
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BUN	blood urea nitrogen
Ca	calcium
CCA	Cholangiocarcinoma
CEA	carcinoembryonic antigen
CL	total body clearance
Cl	chloride
C_{max}	maximum plasma concentration
CNS	central nervous system
CO_2	carbon dioxide
CPS	combined positive score
CR	complete response
CRT	chemoradiotherapy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EHC	extrahepatic cholangiocarcinoma
EOT	End of Treatment
FGFR2	Fibroblast growth factor receptor 2
FU	follow up
GBC	gallbladder carcinoma
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GRAS	Generally Regarded as Safe
HBV	Hepatitis B Virus
hCG	human chorionic gonadotrophin

Abbreviation	Definition
HCO_3	Bicarbonate
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IdH1	Isocitrate dehydrogenase 1
IEC	Independent Ethics Committee
IHC	intrahepatic cholangiocarcinoma
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IV	Intravenous
K	Potassium
KPC	Kras, p53, and Cre cell line used in a mouse model of pancreatic cancer
LDH	lactate dehydrogenase
Mg	Magnesium
mPDAC	metastatic pancreatic ductal adenocarcinoma
MRI	magnetic resonance imaging
Na	Sodium
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PDX	patient derived xenograft
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
QTcF	QT interval corrected using the Fridericia method
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SoC	standard of care
$t_{1/2}$	terminal phase half-life
TEAE	treatment emergent adverse events
TG	tumor graft
TK	toxicokinetics
T_{max}	time to reach maximum plasma concentration
USPI	United States Package Insert

Abbreviation	Definition
USP/NF	United States Pharmacopeia/National Formulary
Vd	volume of distribution
WOCBP	women of childbearing potential

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3. SCHEDULE OF ASSESSMENTS: HEAD AND NECK SQUAMOUS CELL CARCINOMA

Study Flow	Screening Period	Run-In (RI) Period	Cycle 1	Each Subsequent Cycle	End of Treatment Visit (EOT)	Follow up (FU) Period
Days	Days -28 to Day -1 prior to Randomization	RI Day 1 to Day 3 (72 hours)	Day 1	Every 21 ± 3 days	EOT: 30 ± 7 days after last dose	Every 12 ± 4 weeks after EOT visit
Sign Informed Consent	X					
Eligibility Criteria[a]	X					
Medical History[b]	X					
Prior Cancer Therapy[c]	X					
Obtain biopsy (optional)	X[d]				X[e]	
Physical Examination[f]	X[g]					
Targeted Physical Exam		X[h]	X[i]	X[i]	X	
Prior/Concomitant medications	X		X	X	X	
Height	X					
Weight[j]	X	X	X	X	X	
Vital Signs[k]	X	X	X	X	X	
12-lead ECG[l]	X	X	X	X[m]		
ECOG Performance Status	X		X[n]	X[n]	X	

[a] Assessed during screening and confirmed prior to randomization
[b] Includes previous major medical history (e.g., diabetes, cardiovascular disease, major chronic diseases and corresponding treatments, previous surgical history (e.g., diagnostic, or therapeutic invasive surgery)
[c] Includes histological diagnosis, pathological classification, clinical staging, genetic mutation results (if applicable), and treatment history
[d] Archival core biopsy tissue (if available) or fresh core biopsy tissue if archival tissue is unavailable (optional)
[e] Fresh core biopsy tissue (optional)
[f] Physical exam to be performed within 24 hours prior to time of dosing
[g] Includes examination of head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, joints, extremities, neurological, and skin
[h] Does not need to be completed if performed during screening less than 72 hours before randomization
[i] Physical exam to be performed within 24 hours prior to time of dosing
[j] Weight can be obtained within 24 hours prior to dosing.
[k] Measure vital signs pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
[l] Performed locally; on dosing days collected 15 minutes ± 5 minutes after IP administration
[m] Day 1 of Cycles 3 and 6
[n] Within 24 hours of dosing

Study Flow	Screening Period	Run-In (RI) Period	Cycle 1	Each Subsequent Cycle	End of Treatment Visit (EOT)	Follow up (FU) Period
Days	Days -28 to Day -1 prior to Randomization	RI Day 1 to Day 3 (72 hours)	Day 1	Every 21 ± 3 days	EOT: 30 ± 7 days after last dose	Every 12 ± 4 weeks after EOT visit
Assess CPS score[o]	X					
Pregnancy test (WOCBP only)[p]	X	X	X	X	X	
Clinical chemistry labs[q]	X	X[r]	X	X	X	
Clinical hematology labs[s]	X	X[r]	X	X	X	
PT/aPTT/INR[t]	X					
Tumor assessment	X[u]			X[v]	X[w]	
Randomization		X				
Adverse Events Assessment[x]	X	X	X	X	X	
Pharmacokinetic evaluation		X	X	X[y]		
LSTA1/placebo administration		X	X	X		
Paclitaxel administration			X	X		

[o] Combined Positive Score assessed from pathology result
[p] Serum or urine to be done at screening visit, repeated within 24 hours prior to first dose of study drug, and within 24 hours prior to administration of study drug, and at EOT; performed locally
[q] Within 72 hours prior to dosing: Na, K, Cl, Mg, Ca, HCO_3/CO_2, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH; performed locally
[r] Screening labs do not need to be repeated if performed within 72 hours prior to the run-in dose
[s] Within 72 hours prior to dosing: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets; performed locally
[t] Performed locally
[u] The initial tumor imaging will be performed within 28 days before randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before randomization. The same imaging technique should be used for a subject throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management.
[v] CT/MRI chest, abdomen, pelvis, and all clinically indicated sites; Every 8 weeks (±7 days) from C1D1 up to and including Week 52, then every 12 weeks (±7 days) until disease progression. For subjects who discontinue study treatment for reasons other than radiographic PD, follow-up scans should be performed every 8 weeks (±7 days) up to and including Week 52, then every 12 weeks until PD, EOT visit, lost to follow-up, or withdrawal of consent. Use same imaging method as was used at screening/baseline.
[w] If scan was obtained within 4 weeks prior to the EOT visit, then a scan at EOT visit is not mandatory. For subjects who discontinue study drug without confirmed disease progression, a radiologic evaluation should be repeated at the time of treatment discontinuation (i.e., date of discontinuation ± 4-week window).
[x] Assessed using CTCAE v. 5.0
[y] At visits through Day 1 of Cycle 6; see Table 12 for timepoints

Study Flow	Screening Period	Run-In (RI) Period	Cycle 1	Each Subsequent Cycle	End of Treatment Visit (EOT)	Follow up (FU) Period
Days	Days -28 to Day -1 prior to Randomization	RI Day 1 to Day 3 (72 hours)	Day 1	Every 21 ± 3 days	EOT: 30 ± 7 days after last dose	Every 12 ± 4 weeks after EOT visit
Post-study anti-cancer therapy status						X
Overall Survival[z]						X

[z] Can be conducted by visit, phone contact, or record review

4. SCHEDULE OF ASSESSMENTS: 1L CHOLANGIOCARCINOMA

Study Flow	Screening Period	Run-In (RI) Period	First 8 Cycles		Cycles 9 and Beyond	End of Treatment Visit (EOT)	Follow up (FU) Period
			Every 21 days		Every 28 days		
Days	Days -28 to Day -1 prior to Randomization	RI Day 1 to 3 (72 hours)	Day 1 ± 3 Days	Day 8 ± 1 Day	Day 1 ± 3 Days	EOT: 30 ± 7 days after last dose	Every 12 ± 4 weeks after EOT visit
Sign Informed Consent	X						
Eligibility Criteria[a]	X						
Medical History[b]	X						
Prior Cancer Therapy[c]	X						
Obtain biopsy (optional)	X[d]					X[e]	
Physical Examination	X[f]						
Targeted Physical Exam		X[g]	X[h]	X[h]	X[h]	X	
Prior/Concomitant medications	X		X	X	X	X	
Height	X						
Weight[i]	X	X	X	X	X	X	
Vital Signs[j]	X	X	X	X	X	X	
12-lead ECG[k]	X	X	X[l]				
ECOG Performance Status	X		X[m]	X[m]	X[m]	X	

[a] Assessed during screening and confirmed prior to randomization
[b] Includes previous major medical history (e.g., diabetes, cardiovascular disease, major chronic diseases and corresponding treatments, previous surgical history (e.g., diagnostic, or therapeutic invasive surgery)
[c] Includes histological diagnosis, pathological classification, clinical staging, genetic mutation results (if applicable), and treatment history
[d] Archival core biopsy tissue (if available) or fresh core biopsy tissue if archival tissue is unavailable (optional)
[e] Fresh core biopsy tissue (optional)
[f] Includes examination of head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, joints, extremities, neurological, and skin
[g] Does not need to be completed if performed during screening less than 72 hours before randomization
[h] Physical exam to be performed within 24 hours prior to time of dosing
[i] Weight can be obtained within 24 hours prior to dosing
[j] Measure vital signs pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
[k] Performed locally; on dosing days collected 15 minutes ± 5 minutes after IP administration
[l] Day 1 of Cycles 1, 3, and 6
[m] Within 24 hours of dosing

Study Flow	Screening Period	Run-In (RI) Period	First 8 Cycles		Cycles 9 and Beyond	End of Treatment Visit (EOT)	Follow up (FU) Period
			Every 21 days		Every 28 days		
Days	Days -28 to Day -1 prior to Randomization	RI Day 1 to 3 (72 hours)	Day 1 ± 3 Days	Day 8 ± 1 Day	Day 1 ± 3 Days	EOT: 30 ± 7 days after last dose	Every 12 ± 4 weeks after EOT visit
Assess CPS score[n]	X						
Pregnancy test (WOCBP only)[o]	X	X	X	X	X	X	
Clinical chemistry labs[p]	X	X[q]	X		X	X	
Clinical hematology labs[r]	X	X[q]	X[q]	X[q]	X	X	
PT/aPTT/INR[s]	X						
Tumor biomarker assessment[t]		X	X		X	X	
Tumor assessment	X[u]		X[v]		X[v]	X[w]	
Randomization		X					
Adverse Events Assessment[x]	X	X	X	X	X	X	

[n] Combined Positive Score assessed from pathology result (if available)
[o] Serum or urine to be done at screening visit, repeated within 24 hours prior to first dose of study drug, and within 24 hours prior to administration of study drug, and at EOT; performed locally
[p] Within 72 hours of dosing: Na, K, Cl, Mg, Ca, HCO_3/CO_2, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH; performed locally
[q] Screening labs do not need to be repeated if performed within 72 hours prior to the run-in dose
[r] Within 72 hours of dosing: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets; performed locally
[s] Performed locally
[t] Within 72 hours of dosing: biomarker assessments for CA19-9, CEA, and CA125; performed locally
[u] The initial tumor imaging will be performed within 28 days before randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before randomization. The same imaging technique should be used for a subject throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management.
[v] CT/MRI chest, abdomen, pelvis, and all clinically indicated sites; Every 8 weeks (±7 days) from C1D1 up to and including Week 52, then every 12 weeks (±7 days) until disease progression. For subjects who discontinue study treatment for reasons other than radiographic PD, follow-up scans should be performed every 8 weeks (±7 days) up to and including Week 52, then every 12 weeks until PD, EOT visit, lost to follow-up, or withdrawal of consent. Use same imaging method as was used at screening/baseline. If imaging shows disease progression, then another tumor assessment should be performed 4 to 6 weeks later to confirm progression.
[w] If scan was obtained within 4 weeks prior to the EOT visit, then a scan at EOT visit is not mandatory. For subjects who discontinue study drug without confirmed disease progression, a radiologic evaluation should be repeated at the time of treatment discontinuation (i.e., date of discontinuation ± 4-week window).
[x] Assessed using CTCAE v. 5.0

Study Flow	Screening Period	Run-In (RI) Period	First 8 Cycles		Cycles 9 and Beyond	End of Treatment Visit (EOT)	Follow up (FU) Period
			Every 21 days		Every 28 days		
Days	Days -28 to Day -1 prior to Randomization	RI Day 1 to 3 (72 hours)	Day 1 ± 3 Days	Day 8 ± 1 Day	Day 1 ± 3 Days	EOT: 30 ± 7 days after last dose	Every 12 ± 4 weeks after EOT visit
Pharmacokinetic evaluation		X	X[y]				
LSTA1/placebo administration		X	X	X	X		
Cisplatin/gemcitabine administration			X	X			
Durvalumab administration			X		X		
Post-study anti-cancer therapy status							X
Overall Survival[z]							X

[y] At visits through Day 1 of Cycle 6; see Table 12 for timepoints
[z] Can be conducted by visit, phone contact, or record review

5. SCHEDULE OF ASSESSMENTS: 2L CHOLANGIOCARCINOMA

Study Flow	Screening Period	Run-In (RI) Period	Every 14 ± 3 days	End of Treatment Visit (EOT)	Follow up (FU) Period
Days	Days -28 to Day -1 prior to Randomization	RI Day 1 to 3 (72 hours)	Day 1	EOT: 30 ± 7 days after last dose	Every 12 ± 4 weeks after EOT visit
Sign Informed Consent	X				
Eligibility Criteria[a]	X				
Medical History[b]	X				
Prior Cancer Therapy[c]	X				
Obtain biopsy (optional)	X[d]			X[e]	
Physical Examination	X[f]				
Targeted Physical Exam		X[g]	X[h]	X	
Prior/Concomitant medications	X		X	X	
Height	X				
Weight[i]	X	X	X	X	
Vital Signs[j]	X	X	X	X	
12-lead ECG[k]	X	X	X[l]		
ECOG Performance Status	X		X[m]	X	

[a] Assessed during screening and confirmed prior to randomization
[b] Includes previous major medical history (e.g., diabetes, cardiovascular disease, major chronic diseases and corresponding treatments, previous surgical history (e.g., diagnostic, or therapeutic invasive surgery)
[c] Includes histological diagnosis, pathological classification, clinical staging, genetic mutation results (if applicable), and treatment history
[d] Archival core biopsy tissue (if available) or fresh core biopsy tissue if archival tissue is unavailable (optional)
[e] Fresh core biopsy tissue (optional)
[f] Includes examination of head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, joints, extremities, neurological, and skin
[g] Does not need to be completed if performed during screening less than 72 hours before randomization
[h] Physical exam to be performed within 24 hours prior to time of dosing
[i] Weight can be obtained within 24 hours prior to dosing
[j] Measure vital signs pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
[k] Performed locally; on dosing days collected 15 minutes ± 5 minutes after IP administration
[l] Day 1 of Cycles 1, 3, and 6
[m] Within 24 hours of dosing

Study Flow	Screening Period	Run-In (RI) Period	Every 14 ± 3 days	End of Treatment Visit (EOT)	Follow up (FU) Period
Days	Days -28 to Day -1 prior to Randomization	RI Day 1 to 3 (72 hours)	Day 1	EOT: 30 ± 7 days after last dose	Every 12 ± 4 weeks after EOT visit
Assess CPS score[n]	X				
Pregnancy test (WOCBP only)[o]	X	X	X	X	
Clinical chemistry labs[p]	X	X[q]	X	X	
Clinical hematology labs[r]	X	X[q]	X[q]	X	
PT/aPTT/INR[s]	X				
Tumor biomarker assessment[t]		X	X	X	
Tumor assessment	X[u]		X[v]	X[w]	
Randomization		X			
Adverse Events Assessment[x]	X	X	X	X	
Pharmacokinetic evaluation		X	X[y]		

[n] Combined Positive Score assessed from pathology result (if available)
[q] Serum or urine to be done at screening visit, repeated within 24 hours prior to first dose of study drug, and within 24 hours prior to administration of study drug, and at EOT; performed locally
[p] Within 72 hours of dosing: Na, K, Cl, Mg, Ca, HCO_3/CO_2, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH; performed locally
[q] Screening labs do not need to be repeated if performed within 72 hours prior to the run-in dose
[r] Within 72 hours of dosing: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets; performed locally
[s] Performed locally
[t] Within 72 hours of dosing: biomarker assessments for CA19-9, CEA, and CA125; performed locally
[u] The initial tumor imaging will be performed within 28 days before randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before randomization. The same imaging technique should be used for a subject throughout the study. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management.
[v] CT/MRI chest, abdomen, pelvis, and all clinically indicated sites; Every 8 weeks (±7 days) from C1D1 up to and including Week 52, then every 12 weeks (±7 days) until disease progression. For subjects who discontinue study treatment for reasons other than radiographic PD, follow-up scans should be performed every 8 weeks (±7 days) up to and including Week 52, then every 12 weeks until PD, EOT visit, lost to follow-up, or withdrawal of consent. Use same imaging method as was used at screening/baseline. If imaging shows disease progression, then another tumor assessment should be performed 4 to 6 weeks later to confirm progression.
[w] If scan was obtained within 4 weeks prior to the EOT visit, then a scan at EOT visit is not mandatory. For subjects who discontinue study drug without confirmed disease progression, a radiologic evaluation should be repeated at the time of treatment discontinuation (i.e., date of discontinuation ± 4-week window).
[x] Assessed using CTCAE v. 5.0
[y] At visits through Day 1 of Cycle 6; see Table 12 for timepoints

Study Flow	Screening Period	Run-In (RI) Period	Every 14 ± 3 days	End of Treatment Visit (EOT)	Follow up (FU) Period
Days	Days -28 to Day -1 prior to Randomization	RI Day 1 to 3 (72 hours)	Day 1	EOT: 30 ± 7 days after last dose	Every 12 ± 4 weeks after EOT visit
LSTA1/placebo administration		X	X		
Oxaliplatin, folinic acid, and fluorouracil administration[z]			X		
Post-study anti-cancer therapy status					X
Overall Survival[aa]					X

[z] Fluorouracil administration continues through day 3 via a 46-hour continuous infusion
[aa] Can be conducted by visit, phone contact, or record review

6. BACKGROUND AND SIGNIFICANCE

6.1 Head and Neck Squamous Cell Carcinoma and Cholangiocarcinoma

Head and neck cancer is the seventh most common cancer in the world, with 1.1 million new diagnoses reported annually.[1] Head and neck cancer accounts for about 4% of all cancers in the United States. This year, an estimated 66,470 people (48,520 men and 17,950 women) will be diagnosed with head and neck cancer. It is estimated that 15,050 deaths (10,940 men and 4,110 women) from head and neck cancer will occur in the United States this year. In 2020, an estimated 277,597 people worldwide died from the disease.[*†]

More than 90% of head and neck cancers are squamous cell carcinomas (HNSCC) that arise from the mucosal surfaces of the oral cavity oropharynx, and larynx.[2] Oral cavity and larynx cancer risk factors include tobacco consumption, alcohol abuse or both, whereas pharynx cancers are increasingly attributed to infection with human papillomavirus (HPV), primarily HPV-16. Most patients are diagnosed with late-stage HNSCC without a clinically evident antecedent pre-malignant lesion.

Treatment for HNSCC is generally multimodal, consisting of surgery followed by chemoradiotherapy (CRT) for oral cavity cancers and primary CRT for pharynx and larynx cancers. The epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab is generally used in combination with radiation in HPV-negative HNSCC where comorbidities prevent the use of cytotoxic chemotherapy. Immune checkpoint inhibitors pembrolizumab and nivolumab are approved for treatment of recurrent or metastatic HNSCC and pembrolizumab as primary treatment for unresectable disease.[3] Despite improvements in treatment options, particularly with the incorporation of immune checkpoint inhibitors to the standard of care (SoC), the overall survival (OS) of patients with advanced HNSCC remains poor.

Cholangiocarcinoma (CCA) includes cancer of the intrahepatic bile ducts, perihilar and distal extrahepatic bile ducts, and the gallbladder. There were an estimated 12,190 new diagnoses and 3,790 deaths from gallbladder and extrahepatic bile duct cancer in the United States in 2018.[4] Biliary tract cancers usually present at an advanced stage, and only approximately 20% of tumors are considered resectable. CCA is a rare tumor type that accounts for less than 1% of all human cancers.

CCA is a heterogeneous disease arising from the biliary epithelium. In most parts of the world, particularly the Western countries, the peak age of incidence for CCA is the seventh decade and the disease affects both genders, with a slight male preponderance. CCA represents an estimated 3% of all gastrointestinal (GI) system malignancies and are classically subdivided into three groups depending on the anatomical site of origin: intrahepatic, perihilar CCA and distal

[*] Cancer Facts & Figures 2022. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html
[†] National Cancer Institute. https://www.cancer.gov/

CCA. Multiple studies have shown rising rates of intrahepatic CCA although medical coding and misclassification may confound the true incidence.

Risk factors for CCA include bile duct cysts, primary sclerosing cholangitis, cholelithiasis, cirrhosis, viral hepatitis, and hemochromatosis.[5]

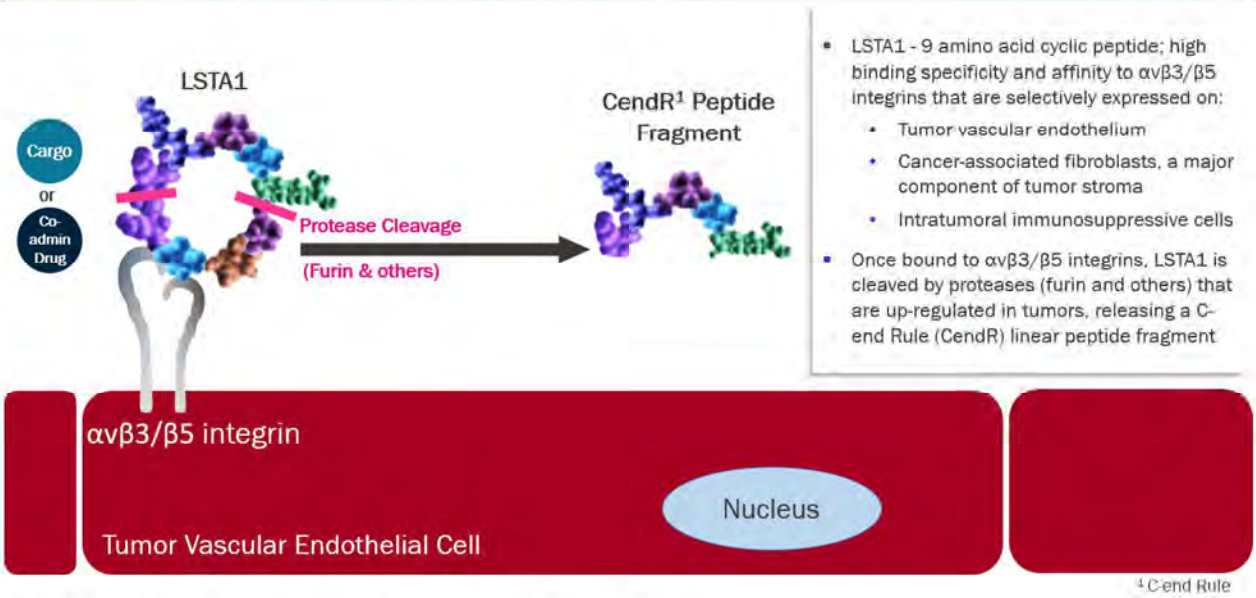
Surgical resection with negative margins is the only potentially curative treatment for CCA. Surgical resection is only feasible for ~ 30% of patients and recurrence after surgery is frequent. In ~70% of patients, the disease is unresectable or metastatic at the time of diagnosis. For these patients, treatment options are limited to systemic chemotherapy, immunotherapy, and targeted therapy for advanced metastatic cancers with specific gene mutations [e.g., Fibroblast growth factor receptor 2 (FGFR2) and Isocitrate dehydrogenase 1 (IDH1)].[6] After progression on 1L treatment of unresectable or metastatic CCA, treatment regimens typically include fluorouracil, gemcitabine, or targeted therapies with median time to progression with these regimens ranging from 1.6 to 5.5 months.[7]

Despite advances in drug development, robotic surgery, radiotherapy, immunotherapy, and molecular characterization of human cancers including HNSCC and CCA, outcomes have remained relatively unchanged for the past few years. Most patients still present with advanced-stage disease, have limited treatment options in the metastatic disease setting, and suffer high morbidity and low survival rates. There exists a significant unmet medical need for more effective treatment options that improve OS.

This study will include patients with advanced solid tumors. Specifically, this study will include patients with advanced HNSCC who have progressed after 1L immunotherapy, patients with CCA who have not received prior systemic chemotherapy or targeted therapy or loco-regional therapy (including but not limited to transarterial chemoembolization, transarterial embolization, transarterial chemotherapy or transarterial radioembolization), and patients with CCA who have progressed on 1L treatment (see eligibility criteria). These patients will be treated with their respective SoC chemotherapy regimens ± LSTA1 or LSTA1 matching placebo. These specific patient populations were chosen as they are areas of significant unmet medical need and because their tumor physiology and microenvironment may be amenable to the LSTA1 mechanism of action. These solid tumors all exhibit varying degrees of desmoplasia (i.e., the presence of fibrotic stroma that surrounds and infiltrates the tumor structures).[8, 9] LSTA1 selectively activates a transport pathway to overcome this obstacle thereby improving drug delivery and tumor concentration of co-administered chemotherapeutic agents. A Phase 1 clinical trial of LSTA1 in combination with nab-paclitaxel and gemcitabine in another advanced solid tumor with dense stroma (metastatic pancreatic ductal adenocarcinoma) has demonstrated safety and preliminary efficacy with no dose limiting toxicities.

6.2 LSTA1

The LSTA1 circular peptide [sequence: CRGDKGPDC] homes to tumors through a 3-step process as shown in Figure 1.



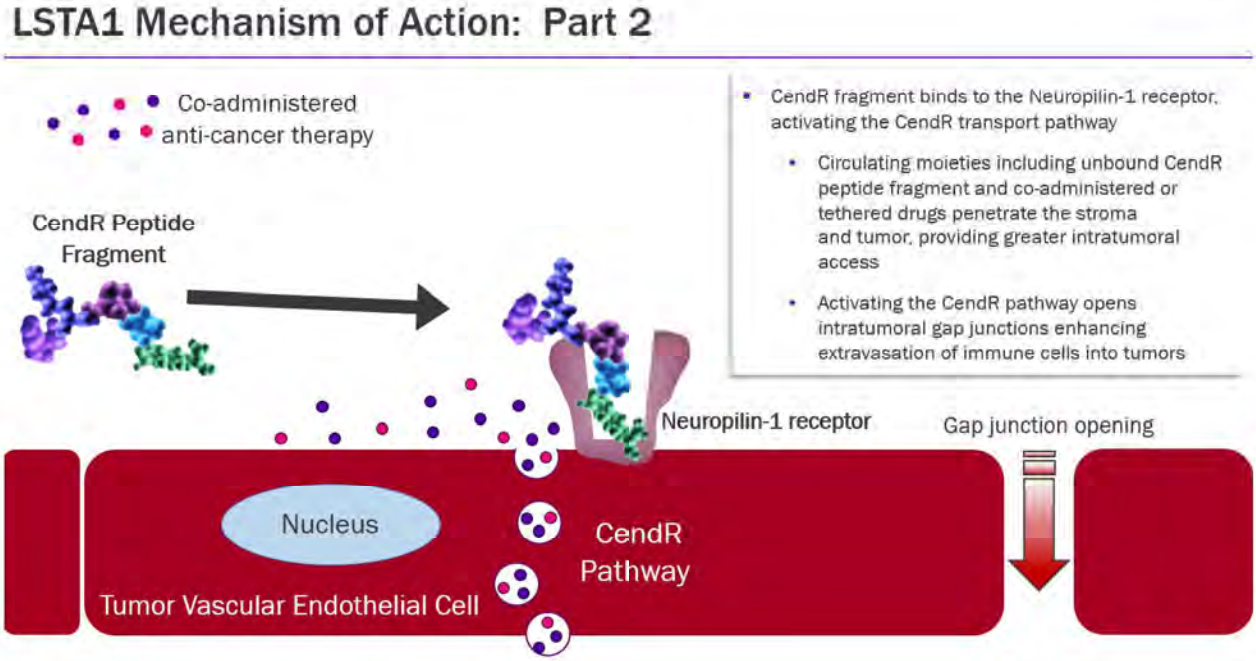


Figure 1. Multistep Binding and Penetration of LSTA1: CendR Trans-Tissue Transport Pathway

First, the integrin binding RGD sequence motif binds to αvβ3 and αvβ5 integrins on tumor endothelium and on tumor cells. Since these integrins are expressed in tumors, but not in normal tissues,[10] the peptide accumulates in tumor vessels in a highly specific manner. The second step involves a protease cleavage after the second basic (K) residue, truncating the peptide to CRGDK. As a result, the CendR fragment of LSTA1 acquires an affinity for neuropilin-1 (the term CendR refers to C-end Rule, the terminally located C required for activity).

In the third step, the CendR motif binds to neuropilin-1 (NRP1), activating an endocytotic/exocytotic transport pathway, the CendR- pathway.[11-13]

The CendR endocytic vesicles can accommodate payloads ranging from small molecules to nanoparticles in size. A remarkable feature of the CendR system is that it can transport payloads co-administered with LSTA1, even when not coupled/conjugated to it.[14-17] An important advantage of the co-administration mode of using LSTA1 is that it does not require chemical modification of the drug to deliver it deeper into tumor tissue. Therefore, in principle, the efficacy of any approved anti-cancer drugs can be improved with LSTA1 without creating a new chemical entity. In addition, unlike conventional targeting, the -drug carrying capacity of the co-administration system is not limited by the availability and quantity of receptors for the homing molecule.[18]

6.3 Findings from Nonclinical Studies

Study reports and publications may refer to LSTA1, CEND-1, or iRGD depending upon where and when the studies were conducted. Therefore, the term LSTA1 and CEND-1 or iRGD are used interchangeably here.

6.3.1 Summary of Pharmacology Studies

The ability of LSTA1 / iRGD in enhancing drug delivery and efficacy has been demonstrated in nonclinical studies in both primary and metastatic tumors in a variety of tumor types of mouse and human origin, as well as genetically modified (KPC) models of pancreatic cancer.[19] The results of these nonclinical studies (more than 30 of them) have demonstrated the improved tumor delivery of several anti-cancer agents, such as nab-paclitaxel, gemcitabine, doxorubicin, cisplatin, trastuzumab, cetuximab, doxorubicin liposomes and irinotecan in silicasomes.[12, 14, 19-21] The intratumor drug concentration increase is generally around 3–5-fold, however the acute increase can be significantly higher, reaching even up to 40-fold.[14] The peak effect with Abraxane has been approximately 12-fold.[14]

In Vivo Studies – Mouse Model Systems

As an example, the following is a summary of *in vivo* efficacy results from three studies in solid tumor mouse models (pancreatic ductal adenocarcinoma, glioblastoma, and hepatocellular carcinoma).

In a study using genetically engineered mouse model of pancreatic ductal adenocarcinoma, the KPC model ($Kras^{G12D/+;}LSL\text{-}Trp53^{R172H/+;}Pdx\text{-}1\text{-}Cre$), the treatment schedule involved 100 mg/kg of gemcitabine, with or without 100 µg iRGD per mouse twice a week.[22] The treatment started when tumors became palpable and were confirmed to be at least 3 mm in diameter by ultrasound imaging (usually at 14–18 weeks of age). The survival difference between the LSTA1/gemcitabine and gemcitabine alone groups was statistically significant ($p = 0.038$; Figure 2).

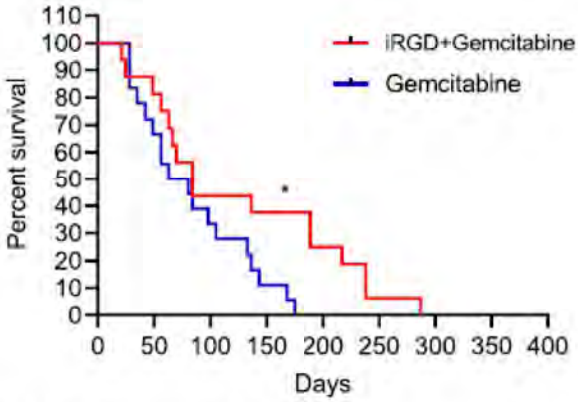


Figure 2. Survival of PDAC-bearing animals
PDAC-bearing animals treated with 100 mg/kg Gemcitabine, with or without 100 µg iRGD twice a week.

A second study assessed the anti-tumor effect of CGKRKD[KLAKLAK]2-nanoparticles alone and co-injected with LSTA1 in the orthotopic glioblastoma 005 (GBM 005) mouse tumor model. CGKRK is a peptide specific for tumor vessels. D[KLAKLAK]2 is a proapoptotic peptide that induces apoptosis by disrupting the mitochondrial membrane. Confocal microscopic analysis showed that the nanoparticles co-injected with LSTA1 spread into the extravascular tumor tissue, whereas without LSTA1, the nanoparticle distribution was limited to tumor vessels. Survival was significantly improved for the LSTA1 combination group.[23]

A third study demonstrated improved drug penetration and therapeutic response to doxorubicin in hepatocellular carcinoma upon LSTA1 co-administration.[17] In a mouse model of endogenously formed hepatocellular carcinomas (TGFa/c-myc mice), LSTA1 significantly increased Evans Blue and doxorubicin penetration into the hepatic tumors, while having no effect in other tissues tested. In addition, the progression of subcutaneous HepG2 human liver cancer xenografts were significantly reduced in mice treated with doxorubicin and LSTA1 as compared with those treated with doxorubicin and control peptide.

In Vivo Studies – Mouse Model using Human Tumor Cells/Tissues

The enhancement of gemcitabine anti-cancer effects by co-administered LSTA1 has been demonstrated in mouse models that used PDAC tumors generated by transplanting cultured human tumor cells (CX models) or human tumor tissue [tumor graft (TG) or PDX models]. Facilitation of NRP-1 dependent drug penetration was observed. LSTA1 and gemcitabine in combination resulted in a significant tumor reduction as compared with gemcitabine without LSTA1. The results were significant in 2 out of 2 cases with CXs and 1 of 3 cases with TGs.[15]

Another study compared the drug delivery efficiency of the LSTA1 combination regimen versus conjugated drug delivery. LSTA1 increased the accumulation of ABX (Nab—paclitaxel) (3 mg/kg) in orthotopic human breast cancer (BT474) and prostate cancer (22Rv1) xenograft models. Three hours after the administration of the drug/LSTA1 combination, tumor concentration of ABX was up to 12-fold higher than when ABX was given alone. LSTA1 also caused ABX penetration farther into the tumor, away from tumor vessels. The ABX/LSTA1

combination inhibited the growth of both BT474 and 22Rv1 tumors, which were essentially resistant to equivalent doses of ABX alone.[14]

The same study also evaluated the anti-tumor effect of doxorubicin co-injected with LSTA1. Combining doxorubicin with LSTA1 resulted in up to 7-fold greater accumulation of doxorubicin in the tumors than when doxorubicin was given alone. LSTA1 given with doxorubicin also potentiated the activity of doxorubicin. LSTA1 alone at the dose used in the combination group showed no effect on tumor growth, supporting the premise that the effect of LSTA1 in the combination is due to improved drug penetration.

The utility of LSTA1 in combination with doxorubicin has also been investigated in intraperitoneal tumor cell models (MKN45P-luc and Lovo-6-luc-1). Fluorescein-labeled LSTA1 was delivered into the peritoneal tumors approximately 5-fold more efficiently than a control peptide, with no accumulation in normal organs. The same effect was observed with co-injected IP dextran.[24]

6.3.2 Summary of Pharmacokinetic Studies

The in vivo PK profile of LSTA1 after a single dose was evaluated in four non-GLP animal studies including Sprague-Dawley rats (Study 64803-16-759), Beagle dogs (Study 64803-16-763), cynomolgus monkeys (Study 64804-16-741) and mice (Study 64804-17-646) following intravenous injection of 1, 5 and 50 mg/kg (rats, dogs, monkeys) or 1.5, 4.5 and 13.5 of LSTA1. Blood samples were collected for PK evaluations at the following time points: pre-dose and 1, 5, 10, 15 and 30 minutes, and 1-, 2- and 6-hours post-dose in rats, dogs, monkeys, and 3, 10, 30 and 90 minutes, and 4- and 8-hours post-dose in mice. The results showed typical intravenous profiles that were comparable in all species. The systemic exposure of LSTA1, expressed as maximum plasma concentration (C_{max}) and AUC_{last}, generally increased with dose in a more than dose proportional manner. The average half-lives were approximately 25 minutes in mice, 30 minutes in rats, 40 minutes in dogs and 55 minutes in monkeys. No test-article related clinical observations were noted in any of the animal species tested. These results indicate a favorable in vivo PK profile of LSTA1 after intravenous administration. The PK results of the non-GLP mouse and monkey studies, as well as the Day 1 PK/Toxicokinetic (TK) results of the rat and dog GLP studies are summarized in Table 1.

Table 1. Derived mean pharmacokinetic parameters for LSTA1

Species / Study No.	Mouse / 64804-17-646 (non-GLP)			Rat / 64803-17-386 (GLP)					
No./sex	3M	3M	3M	6M	6F	6M	6F	6M	6F
Dose (mg/kg)	1.5	4.5	13.5	1	1	5	5	75	75
$T_{1/2}$ (h)	0.306	0.344	0.547	0.805	0.248	0.46	0.437	0.341	0.391
C_0 (ng/mL)	10343	40291	68358	4230	3983	24333	28400	469000	436333
Vz obs (mL/kg)	449	599	1007	648	201	366	323	171	254
AUC_{inf} (hr*ng/mL)	1476	3695	10569	1770	1751	9058	9747	215476	166331
Species / Study No.	**Monkey / 64804-16-741 (non-GLP)**			**Dog / 64803-17-469 (GLP)**					
No./sex	3M	3M		3M	3F	3M	3F	5M	5F
Dose (mg/kg)	5	50		1	1	5	5	75	75
$T_{1/2}$ (h)	0.888	0.956		0.665	0.668	0.655	0.648	0.615	0.62
C_0 (ng/mL)	55084	602161		6010	4777	30200	25133	461000	475800
Vz obs (mL/kg)	228	178		241	253	230	230	204	208
AUC_{inf} (hr*ng/mL)	28230	421119		4030	3946	20617	20443	326748	323936

PK parameters for LSTA1 in mouse, rat, dog, and monkey plasma after single intravenous injection. The concentrations of the LSTA1 were used to calculate PK parameters by employing a noncompartmental analysis (Phoenix™ WinNonlin®, version 6.1).

The whole-body distribution and tissue penetration of FAB-labelled iRGD in tumor-bearing mice has been studied by Sugahara.[12] FAM-iRGD accumulated, as seen by a strongly fluorescent signal, in tumor tissue and/or bound to tumor cells in every model tested; these include orthotopic xenografts of prostate, pancreatic ductal, and breast cancer, bone and brain xenografts of prostate carcinoma, and genetically engineered models of de novo pancreatic neuroendocrine (islet), pancreatic ductal, and cervical cancer. The only normal / healthy tissues that stained positive for RGD were kidney (moderate signal) and the bladder (strong signal), indicating elimination via urine.

In a study investigating potential PK interactions (Study MVS2012-ASP01), there were no consistent and significant effects on the gemcitabine exposure by LSTA1, nor was the LSTA1 PK affected by gemcitabine co-administration.

6.3.3 Summary of Toxicology Studies

Preliminary PK and/or non-GLP toxicology studies in CD-1 mice, Sprague Dawley rats, Beagle dogs and cynomolgus monkeys used LSTA1 doses ranging from 1 to 13.5 mg/kg in CD-1 mice, and from 1 to 50 mg/kg in Sprague Dawley rats, Beagle dogs and cynomolgus monkeys. There were no significant differences in the PK profiles, and LSTA1 was well tolerated in all species. Based on these results, rats and dogs were the species chosen for the GLP toxicology studies.

The pivotal studies completed at this time comprise the GLP toxicology study 64803-17-386 in Sprague Dawley rats and the GLP toxicology study 64803-17-469 in Beagle dogs, both

evaluating the potential toxicity of LSTA1 following weekly intravenous injection of LSTA1 for 5 times within one month.

GLP toxicology study 64803-17-386 evaluated the potential toxicity of LSTA1 in Sprague Dawley rats following intravenous injection of 1, 5 and 75 mg/kg on Study Days 1, 8, 15, 22 and 29, and assessed the reversibility, progression and/or potential delayed effects during a 2-week recovery period. In addition, the toxicokinetic profile of LSTA1 in rats was characterized in this study. The results indicated that LSTA1 given in weekly intravenous injections at doses up to 75 mg/kg/day for one month (on Days 1, 8, 15, 22 and 29) to male and female Sprague-Dawley rats was well tolerated. There were no LSTA1 -related clinical signs, or changes in Functional Observation Battery (FOB), body weights, food consumption, ophthalmology, clinical pathology parameters, gross pathology, organ weights or histopathology. Therefore, the no-observed-adverse-effect levels (NOAEL) is defined as 75 mg/kg/day in the study. At 75 mg/kg/day, the C_{max} and AUC_{last} on Day 29 for males were 510333 ng/mL and 199336 hr*ng/mL, respectively, and for females were 494000 ng/mL and 170812 hr*ng/mL, respectively.

GLP toxicology study 64803-17-469 evaluated the potential toxicity of LSTA1 in Beagle dogs following 5 weekly intravenous injections of LSTA1 within one month (on Days 1, 8, 15, 22 and 29). In this study, doses up to 75 mg/kg were well tolerated and did not cause any mortality or moribundity. As with rats, there were no LSTA1 -related changes in clinical observations, body weights, food consumption, body temperature, blood pressure, electrocardiogram (ECG), ophthalmology, clinical pathology, gross pathology, organ weights or histopathology. Therefore, the NOAEL in this study is 75 mg/kg/dose, which corresponds to LSTA1 plasma AUC_{last} values of 390,260 and 398,051 hr*ng/mL, and C_{max} values of 442,200 and 515,800 ng/mL for males and females, respectively.

No separate Safety Pharmacology studies have been conducted but the integrated readouts as part of GLP toxicology studies (Functional Observational Battery in rats and ECG/blood pressure in dogs) did not indicate any effects on the pivotal organ systems. No assessments yet have been conducted for the genetic toxicity or for effects on embryofetal development.

6.3.4 Immunogenicity

Low molecular weight compounds such as LSTA1 are immunogenic only if covalently bound to proteins to form hapten-protein complexes (FDA Guidance: Immunotoxicology Evaluation of Investigational New Drugs). Nevertheless, the potential for immunogenicity of LSTA1 was evaluated in GLP studies using rats (Study 64805-17-430) and dogs (Study 64805-17-445) sera (pre-dose, D7, D29, D44). In the rat study, out of 146 tested for immunogenicity, 3 samples were confirmatory positive, all from different animals. In the dog study, no sample was tested positive. It was concluded that the three rats showing transient positive results on anti-drug antibody analysis were not biologically relevant. Moreover, there were no abnormal findings (such as an altered toxicokinetic profile) that can be attributed to a possible immunogenicity. The results indicate that LSTA1 had a low potential for biologically relevant immunogenicity in both animal species.

6.4 Findings from Clinical Studies

6.4.1 CEND1-001 A Phase 1 Trial of CEND-1 in Combination with Nab-Paclitaxel and Gemcitabine in Metastatic Exocrine Pancreatic Cancer

Only one clinical trial in advanced solid tumors has been completed to date.

In CEND1-001, LSTA1 was given initially at escalating doses from 0.2 mg/kg to 3.2 mg/kg during a run-in period of 1 to 7 days, during which PK and safety of the single agent were assessed.

There were 8 patients in Cohort 1a: 1 patient at dose level 1 (LSTA1 0.2 mg/kg), 1 patient at dose level 2 (0.8 mg/kg), 3 patients at dose level 3 (1.6 mg/kg) and 3 patients at dose level 4 (3.2 mg/kg). There were 23 patients in Cohort 1b, 11 patients at dose level 3 (1.6 mg/kg), 11 patients at dose level 4 (3.2 mg/kg), and 1 patient who was assigned to dose level 4 (3.2 mg/kg) but withdrew from the study following the run-in period and only received the run-in dosing with LSTA1 0.2 mg/kg.

Of the 31 patients enrolled, 29 were evaluated for efficacy, 31 were evaluated for PK and 30 were evaluated for progressive disease (PD) (N = 14 at the 1.6 mg/kg LSTA1 dose and N = 14 at the 3.2 mg/kg LSTA1 dose level, not including the 2 patients in the LSTA1 low dose group). There were 10 patient deaths reported during the study, 9 caused by progression of primary disease (metastatic pancreatic cancer) and 1 due to a left middle cerebral artery stroke.

Confirmed objective responses occurred in 17/29 (58.6%) patients (95% CI = 38.9, 76.5). The objective response rates (ORR) for patients treated with LSTA1 1.6 mg/kg and 3.2 mg/kg were 50% (7/14) and 61.5% (8/13) (61.5%), respectively. Disease control was defined as CR + PR + SD > 16 weeks and the disease control rate (DCR) was 64.3% (9/14) in the LSTA1 1.6 mg/kg group and 92.3% (12/13) in the LSTA1 3.2 mg/kg group.

6.4.2 LSTA1 Pharmacokinetics

Overall, the median T_{max} for LSTA1 was 0.067 hours over all days of PK sampling (minimum was 0.03, maximum 0.55). There was dose proportional increase in C_{max} without increase with repeat dosing.

Assessment of plasma LSTA1 parameters demonstrated that exposure ($AUC_{0\text{-}t}$, $AUC_{0\text{-}6h}$, and $AUC_{0\text{-}inf}$) followed the same pattern described for C_{max} with a trend to increase with increased dose. Dose normalized PK parameters ($AUC_{0\text{-}t/D}$, $AUC_{0\text{-}6h/D}$, and $AUC_{0\text{-}inf/D}$) were similar between visits and doses.

LSTA1 was eliminated with median $T_{1/2}$ values between 1.6 hours and 1.8 hours over all days of PK sampling. CL mean values were between 106.8 mL/h/kg and 266.5 mL/h/kg. The terminal volume of distribution (Vz) mean values were between 220.9 mL/kg and 277.4 mL/kg over all days of PK sampling.

6.4.3 LSTA1 Safety

Of the 31 patients in the safety population, 14 received the 1.6 mg/kg dose, 14 received the 3.2 mg/kg dose, 2 patients received 0.2 mg/kg, and 1 received the 0.8 mg/kg dose.

A dose-limiting toxicity (DLT) in the run-in period (LSTA1 monotherapy) was defined as:

- Grade 4 neutropenia lasting ≥ 5 days or Grade 3 or 4 neutropenia with fever and/or infection
- Grade 4 thrombocytopenia (or Grade 3 with bleeding)
- Grade 3 or 4 treatment-related non-hematological toxicity (Grade 3 nausea, vomiting or diarrhea that last > 72 hours despite maximal treatment constitutes a DLT, insufficient treatment will not constitute an exception to the DLT criteria, as this would constitute inadequate conduct of the study)
- Dosing delay greater than 2 weeks due to treatment-emergent AEs or related severe laboratory abnormalities

A DLT in the combination portion of the study was defined as:

- Any side effect that is more severe, longer in duration or more frequent than side effects expected from the nab-paclitaxel and gemcitabine package insert
- Any side effect that is not included in the nab-paclitaxel and gemcitabine package insert that meets the DLT definition of the monotherapy above

There were no DLTs or grade 3 or 4 adverse events at any LSTA1 dose level during the single agent run-in portion of the study and no clinically significant adverse events attributable to LSTA1 were reported.

The majority of TEAEs were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2. The number of reported TEAEs at each grade was similar between LSTA1 dose levels. Overall, the severity of TEAEs did not increase with LSTA1 dose. The most common CTCAE grade 3–4 TEAEs by SoC were blood and lymphatic system disorders. Overall, 22 (71.0%) patients reported SAEs. There was no trend of increasing frequency of SAEs with increasing LSTA1 dose. The most common SAEs by SoC were infections and infestations.

There were 10 deaths reported during the study, 9 caused by progression of the primary disease (metastatic pancreatic cancer) and 1 due to a left middle cerebral artery stroke. This death (Patient 003-002) occurred towards the end of the long term (3-month) follow-up. The patient discontinued the study on 09 July 2019 and died on 07 October 2019.

The safety data for LSTA1 suggest a favorable benefit-risk profile and safety profile. The absence of any LSTA1 monotherapy related SAEs and low frequency of LSTA1 combination

therapy related SAEs supports the continued evaluation of this investigational therapy for metastatic exocrine pancreatic cancer.

6.5 Rationale for Dose and Mode of Administration

A LSTA1 dose of 3.2 mg/kg will be used in this study. Based on preclinical studies and available clinical data, this dose results in an exposure that is within the biologically optimal dose range. Furthermore, 3.2 mg/kg did not cause any Dose Limiting Toxicities (DLTs) in the Phase 1 study, CEND1-001.

LSTA1 is administered by intravenous injection. This mode of administration was selected to enhance the systemic exposure of LSTA1.

7. STUDY OBJECTIVES

7.1 Primary Objective

To evaluate the safety and tolerability of LSTA1 when added to SoC in patients with advanced solid tumors

7.2 Secondary Objectives

To determine the therapeutic effect of LSTA1 when added to SoC in patients with advanced solid tumors on:

- Overall survival (OS)
- 3-month survival
- 6-month survival
- 12-month survival
- Progression-free survival (PFS)
- Duration of response (DOR) in responding patients with measurable disease at baseline
  - Objective response rate (ORR)
  - Duration of response (DOR)

To evaluate the safety profile of LSTA1 when administered as monotherapy during the run-in period.

To evaluate the dose tolerance of SoC therapy when administered along with LSTA1.

7.3 Pharmacodynamic Objectives

For the CCA cohorts, disease biomarkers CA19-9, carcinoembryonic antigen (CEA), and CA125 will be assessed pre-dose (within 72 hours prior to dosing) at run-in and on Day 1 of each Cycle and at EOT.

For all cohorts, retrospective assessment of tissue biomarkers in optional pre-treatment archival tissue (or pre-treatment core biopsy) and on-treatment optional core biopsy will be assessed.

7.4 Pharmacokinetic Objectives

To characterize the PK profile of LSTA1 when administered with standard of care therapies

To characterize the population PK profile of LSTA1 when administered in combination with SoC therapies

8. STUDY DESIGN

This is a Phase 2a, multicenter, randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of LSTA1 when added to SoC versus SoC alone in subjects with advanced solid tumors. The study will consist of a screening period, a run-in period, a treatment period, an end-of-treatment follow-up visit, and a long-term follow up period. On-going survival and subsequent anti-cancer therapies will be assessed during the long-term follow-up.

The study will include 3 cohorts of subjects which include advanced HNSCC, 1L CCA, and 2L CCA.

8.1 Screening Period

Patients who provide informed consent will be screened for eligibility within 28 days prior to beginning the study run-in period. Subjects must meet all inclusion criteria and none of the exclusion criteria to be eligible for this trial. Screening information, including clinical evaluation, laboratory assessments, tumor biomarkers, imaging, archival tumor tissue if available, and pregnancy test for potential subjects should be recorded in the electronic Case Report Form (eCRF), including reasons for ineligibility.

Tests with results that fail eligibility requirements may be repeated **once** during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before randomization will be used to determine subject eligibility. Additionally, a subject who fails screening may repeat the screening process **one time** if the investigator believes there has been a change in eligibility status (e.g., after recovery from an infection).

8.2 Randomization and Run-In Period

Once eligibility is confirmed, subjects will be *randomized 1:1 within their respective tumor type basket arm* to one of the two treatment groups (i.e., SoC + LSTA1 matching placebo vs. SoC + LSTA1). The run-in must occur no more than 28 days after the subject has signed the ICF.

During the 72-hour run-in, subjects will only receive the LSTA1 or placebo components of their randomized treatment regimen; they will not receive SoC chemotherapy. On Day 1 of the run-in,

subjects will either be given LSTA1 or matching placebo as a slow intravenous (IV) push over one minute (± 30 seconds). Safety will be assessed for the duration of the run-in period.

8.3 Treatment Period

The treatment period begins on Cycle 1 Day 1 through the point at which the investigator determines that the subject will be permanently discontinued from study drug.

- For **advanced HNSCC**, the schedule of treatment administration begins with infusion of paclitaxel (175 mg/m^2 over 3 hours followed by a saline flush. Immediately (within 15 minutes) following completion of the post-paclitaxel saline flush, LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be given as a slow IV push over 1 minute (± 30 seconds). These should all be given every 21 days.

- For **advanced 1L cholangiocarcinoma**, durvalumab 1500 mg will be given with chemotherapy (cisplatin and gemcitabine) every 21 days up to 8 cycles followed by durvalumab 1500 mg given as a single agent every 28 days.

  The schedule of treatment administration on Day 1 begins with infusion of durvalumab via IV infusion according to the United States Package Insert (USPI) or relevant local dosing instructions. Cisplatin 25 mg/m^2 IV will then be administered over 30 to 65 minutes followed by a saline flush of the IV line. Immediately (within 15 minutes) following completion of the post-cisplatin saline flush, LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be given as a slow IV push over 1 minute (± 30 seconds). Following another flush of the IV line, gemcitabine 1000 mg/m^2 IV will then be administered over 30 minutes (± 5 minutes) starting no more than 10 minutes after the completion of LSTA1/matching LSTA1 placebo administration.

  On Day 8, Cisplatin 25 mg/m^2 IV will first be administered over 30 to 65 minutes followed by a saline flush of the IV line. Immediately (within 15 minutes) following completion of the post-cisplatin saline flush, LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be given as a slow IV push over 1 minute (± 30 seconds). Following another flush of the IV line, gemcitabine 1000 mg/m^2 IV will then be administered over 30 minutes (± 5 minutes) starting no more than 10 minutes after the completion of LSTA1/matching LSTA1 placebo administration.

  For cycles 9 and beyond, durvalumab 1500 mg will be given via IV according to the USPI or relevant local dosing instructions. Immediately (within 15 minutes) following completion of durvalumab and saline flush, LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be given as a slow IV push over 1 minute (± 30 seconds).

- For **advanced second-line cholangiocarcinoma**, oxaliplatin, l-folinic acid 200 mg/m^2 or 400 mg/m^2 d,l-folinic acid IV, a fluorouracil bolus and fluorouracil continuous 46-hour infusion will be given every 14 days.

The schedule of treatment administration on Day 1 begins with an infusion of both oxaliplatin 85 mg/m² and l-folinic acid 200 mg/m² **or** 400 mg/m² d,l-folinic acid as a 2-hour (± 15 minutes) intravenous infusion. Immediately following the oxaliplatin and l-folinic acid (or d,l-folinic acid) infusion (within 10 minutes), fluorouracil (5-FU) 400 mg/m² will be given as an intravenous bolus over 5 minutes (± 5 minutes). Following the 5-FU bolus (within 10 minutes), LSTA1 (3.2 mg/kg) or matching LSTA1 placebo will be administered as a slow IV push over 1 minute (± 30 seconds). Upon completion of the LSTA1 IV push or matching LSTA1 placebo (within 10 minutes), a continuous infusion (via home-infusion pump) of 5-FU 2400 mg/m² will be administered over 46 hours.

It is recognized that the infusion of anti-cancer drugs can encounter unforeseen interruptions in the clinic setting. If there is an interruption that causes a deviation in the duration of infusion, these will not be considered protocol deviations. The actual duration of infusions should be recorded. PK analyses will be based on actual times recorded for each PK sample drawn.

Dose modifications/reductions of paclitaxel, cisplatin, durvalumab, gemcitabine, oxaliplatin, and 5-FU are allowable to manage toxicities. Every effort should be made to provide maximal supportive therapy prior to implementing a dose reduction. The dose of LSTA1/matching LSTA1 placebo will not be adjusted. Dose re-escalations are permissible per clinical practice.

Tumor assessments will be performed every 8 weeks (± 7 days) from C1D1 until disease progression or a new anti-cancer therapy commences for up to 12 months then every 12 weeks (± 7 days) thereafter until disease progression. Imaging for screening and tumor assessments must be performed using the same imaging modality as the baseline scans. Those who do not progress will continue to have scans for up to 12 months after the last patient is enrolled. For subjects who discontinue study treatment for reasons other than radiographic disease progression, follow-up scans should be performed every 8 weeks (± 7 days) up to and including 12 months, then should have follow-up scans every 12 weeks until disease progression, lost to follow-up, or withdrawal of consent.

Clinical hematology and chemistry laboratory evaluations will be performed within 72 hours of treatment initiation on Day 1 Cycle 1 and at each subsequent cycle.

8.4 End of Treatment Visit

When the subject permanently discontinues study drug for any reason, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF.

8.5 Follow-up Period

The subject's OS status will be assessed for all subjects during the follow-up period. A patient will be deemed lost to follow up when the primary outcome for that patient cannot be obtained by study closure after reasonable efforts from site staff.

8.6 End of Study

The end of the study will occur when all subjects have completed 12 months of survival follow-up, died, withdrawn consent, or been lost-to follow-up, whichever occurs last, or when the study is terminated.

9. STUDY ENDPOINTS

9.1 Efficacy Endpoints

The following endpoints will be used according to regulatory guidance documents on clinical trial endpoints for the approval of cancer drugs and biologics.‡

Overall survival (OS): defined as the interval from first dose to death from any cause, or the date of last known follow-up alive.

Progression-free survival (PFS): defined as the time from the first dose to the date of first objective evidence of radiological disease progression, or death from any cause, whichever comes earlier, censored on the date of last clinical assessment or tumor assessment, whichever is the later event.

Objective response rate (ORR): defined as the number of patients with documented partial or complete response (PR or CR), relative to the screening tumor measurement, divided by the number of patients evaluable for response as defined per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.

Disease control rate (DCR): defined as the number of patients with documented partial response (PR), complete response (CR), and stable disease (SD) lasting ≥ 16 weeks, relative to the screening tumor measurement, divided by the number of patients evaluable for response as defined per RECIST version 1.1 criteria.

Duration of response (DOR): defined as the time from randomization to disease progression or death in patients who achieve CR or PR.

9.2 Safety Endpoints

Incidence of Adverse events: The National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE)§ will be used to grade the intensity of adverse events throughout the study.

‡ Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics FDA. Guidance for Industry. December 2018. https://www.fda.gov/media/71195/download
Guideline on the clinical evaluation of anticancer medicinal products. March 24, 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf
§ https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Frequency of Grade ≥ 3 treatment-related adverse events: defined as the rate of adverse events considered related to LSTA1 which meet the CTCAE Grade ≥ 3 criteria over the duration of the trial.

Frequency of treatment-related serious adverse events (SAEs): defined as the rate of serious adverse events considered related to LSTA1 over the duration of the trial

Electrocardiograms (ECG): a painless test that uses temporary electrodes on the chest and limbs to monitor, track, and document the heart's electrical activity. ECGs will be performed locally.

Clinical laboratory investigations: a blood collection analysis of clinical chemistry and hematology parameters. These parameters include Na, K, Cl, Mg, Ca, HCO_3/CO_2, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, LDH, hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelets, aPTT, PT, and INR.

Physical examinations: a clinical examination of head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, joints, extremities, neurological, skin, weight, and height.

Vital signs: assessment of temperature, blood pressure, pulse rate, and respiratory rate pre-dose (0–120 minutes prior) and post-dose (within 15 minutes).

9.3 Other Analyses

Pharmacokinetic analysis: Plasma samples will be collected and analyzed for PK analysis of LSTA1

Pharmacodynamic analyses:

- For the cholangiocarcinoma (CCA) cohorts, disease biomarkers CA19-9, CEA, and CA125 will be assessed pre-dose (within 72 hours prior to dosing) at run-in and on Day 1 of each Cycle and at EOT.
- Where available, exploratory tissue biomarkers will be evaluated from pre-treatment archival tissue (or fresh core biopsy if archival tissue is unavailable or insufficient for analysis) and from the end of treatment optional core biopsy per clinician judgment.

ECOG Performance analyses:

- ECOG performance status will be collected and analyzed

10. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

10.1 Inclusion Criteria All Subjects

Subjects who meet **ALL** the following criteria are eligible for this study:

1. Subjects must be ≥ 18 years of age at time of consent and provide informed consent
2. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
3. Life expectancy ≥ 3 months, as determined by the investigator
4. At least one bidimensional measurable target lesion assessed by RECIST 1.1. Tumor lesion located in the area of previous radiotherapy or other local and regional treatment sites is generally not a measurable lesion unless there is definite progression of the lesion, or the lesion persists three months after radiotherapy. Additionally, a biopsy site should not be considered a target lesion.
5. Adequate organ and marrow function:
    - Platelets ≥ 100 x 10^9/L (>100,000 per mm^3)
    - WBC ≥ 3000/µL
    - Absolute neutrophil count ≥ 1.5 x 10^9/L
    - Serum albumin ≥ 2.5 g/L
    - ALT and AST ≤ 2.5 x ULN in the absence of liver metastases or < 5 x ULN in the presence of liver metastases
    - Bilirubin ≤ 1.5 x ULN
    - Hemoglobin ≥ 9.0 g/dL. Labs may be drawn 24 hours after a transfusion to meet this criterion.
    - INR < 1.5 (for patients not receiving therapeutic anticoagulation)
    - Adequate respiratory and cardiac function (PaO_2 ≥ 60 mm Hg or oxygen saturation ≥ 92% on room air, and 12-lead ECG with normal tracing or non-clinically significant changes that do not require medical intervention)
    - QT interval corrected using the Fridericia method (QTcF) < 470 ms

6. Adequate contraception:

   - All female patients will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically. Female patients of childbearing potential must agree to use two forms of highly effective contraception methods (a primary and a secondary method – see next bullet) during the study and for a period of 6 months following the last administration of the study drug, unless subject received cisplatin whereby aforementioned contraception methods must be adhered to for 14 months.

   - Male patients and their female partners, who are of childbearing potential and are not practicing total abstinence, must agree to use two forms of highly effective contraception methods (a primary and a secondary method) during the study and for a period of 6 months following the last administration of the study drug, unless subject received cisplatin whereby the following contraception methods must be adhered to for 14 months. These contraception methods include oral, transdermal, systemic or implant contraception birth control, intra-uterine devices (IUD), abstinence and double barrier method such as diaphragm with spermicidal gel or other recommended double barrier methods.

10.2 Inclusion Criteria 2L Head and Neck Squamous Cell Carcinoma (HNSCC)

7. Patients with histologically confirmed recurrent or metastatic HNSCC that is unresectable or considered incurable by local therapies and that has progressed after 1L immunotherapy

   - Characterization of tumor PD-L1 expression using the PD-L1 IHC 22C3 PharmDx Assay
   - Receipt of prior treatment with checkpoint inhibitors as a single agent and have received at least 2 doses of the agent or a minimum of 6 weeks on treatment
   - Have documented clinical or radiographic progression by RECIST 1.1

8. The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx. Patients may **not** have primary tumor sites of the skin, paranasal sinuses, or the nasopharynx (any histology).**

10.3 Inclusion Criteria 1L Cholangiocarcinoma

11. Pathologically confirmed metastatic or unresectable cholangiocarcinoma or gallbladder carcinoma (GBC), with no prior systemic chemotherapy or targeted therapy or loco-regional therapy (including but not limited to transarterial chemoembolization,

** Inclusion criteria 9 and 10 were removed beginning with version 6 of the protocol.

transarterial embolization, transarterial chemotherapy or transarterial radioembolization). Patients with recurrent disease more than 6 months after completion of adjuvant chemotherapy following curative resection are eligible.

a) Includes intrahepatic cholangiocarcinoma (IHC), extrahepatic cholangiocarcinoma (EHC), and GBC, but not ampulla of Vater cancers

b) For liver dominant IHC, disease must comprise < 60% of the liver parenchyma, as defined by the investigator

12. If the patient has had decompression of the biliary tree within the last 14 days, stability of the bilirubin level needs to be confirmed with two measurements that are within 5 to 7 days of each other; (the second measurement must be obtained within 7 days prior to randomization); both the first and second measurement must be ≤ 1.5 x ULN; stability is defined as the second measurement being no more than one point higher than the first measurement

10.4 Inclusion Criteria 2L Cholangiocarcinoma

13. Pathologically confirmed metastatic or unresectable cholangiocarcinoma or GBC

a) Includes intrahepatic cholangiocarcinoma (IHC), extrahepatic cholangiocarcinoma (EHC), and GBC, but not ampulla of Vater cancers

b) For liver dominant IHC, disease must comprise < 60% of the liver parenchyma, as defined by the investigator

14. Clear evidence of progression of disease ***after*** 1L chemotherapy with gemcitabine and immunotherapy (i.e., PD-1/PD-L1 monoclonal antibody treatment), gemcitabine, cisplatin and immunotherapy, or immunotherapy +/- gemcitabine maintenance therapy. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are eligible. If a patient received adjuvant treatment and had disease recurrence after 6 months, they will only be eligible after experiencing disease progression on one line of chemotherapy used to treat the disease recurrence.

15. If the patient has had decompression of the biliary tree within the last 14 days, stability of the bilirubin level needs to be confirmed with two measurements that are within 5 to 7 days of each other; (the second measurement must be obtained within 7 days prior to randomization); both the first and second measurement must be ≤ 1.5 x ULN; stability is defined as the second measurement being no more than one point higher than the first measurement

10.5 Exclusion Criteria for All Subjects

A subject who meets any of the following criteria will be excluded from the study:

1. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results, including but not limited to:
    - Any major surgery or irradiation less than 4 weeks prior to baseline disease assessment
    - Active infection (viral, fungal, or bacterial) requiring systemic therapy
    - Known active HBV, HCV, or HIV infection
    - Active tuberculosis as defined per local guidance
    - History of allogeneic tissue/solid organ transplant
    - Prior malignancy requiring active treatment within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast
    - Pregnant or breastfeeding
    - Clinically significant or symptomatic cardiovascular/cerebrovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before randomization
2. Subjects with a known sensitivity to LSTA1 or its excipients
3. Patients with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent
4. Have received chemotherapy, radiotherapy, biotherapy, endocrine therapy, immunotherapy, and other anti-tumor therapy within 28 days prior to randomization **(not applicable to 2L CCA)**
5. History or clinical evidence of CNS metastases; exceptions include:
    - Subjects who have completed local therapy and who meet both of the following criteria:
        - Subjects must be asymptomatic AND
        - Subjects must have no requirement for steroids 6 weeks prior to start of study treatment. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases

10.6 Exclusion Criteria 2L Head and Neck Squamous Cell Carcinoma (HNSCC)

6. Patients who received prior taxanes unless it was given as part of neoadjuvant, concurrent therapy in the curative intent setting, and it has been more than 6 months since last dose

7. Known allergies to taxanes or their standard pretreatments

8. Any surgery involving the HNSCC for which the patient is being treated (except biopsies) that occurred within 28 days prior to randomization

9. Subjects who cannot discontinue any concomitant medications that are inducers or inhibitors of CYP2C8 (e.g., rifampicin, phenobarbital, secobarbital, phenytoin, clopidogrel, gemfibrozil, zafirlukast, felodipine) or CYP3A4 (e.g., dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin/rifampicin, rifabutin, St. John's Wort, erythromycin, itraconazole, ritonavir, verapamil) during treatment with paclitaxel

10. Creatinine clearance < 45 mL/min (calculated using the Cockcroft-Gault formula below)

    - Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL
    - Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL[††]

10.7 Exclusion Criteria 1L Cholangiocarcinoma

16. Patients who received prior palliative systemic treatment for their advanced cancer

17. Patients with a history of idiopathic pulmonary fibrosis (pneumonitis requiring treatment with steroids), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on baseline imaging

18. Patients with a history of active interstitial lung disease

19. Concurrent use of immunosuppressive medication, EXCEPT for the following:

    a. Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection)

    b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent

[††] Inclusion criteria 11 through 15 were removed beginning with version 6 of the protocol.

c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

20. Active autoimmune disease that might deteriorate when receiving an immune-stimulatory agent. Patients with Type 1 diabetes, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.

21. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)

22. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab. Note: While enrolled, patients should not receive any live vaccines while receiving durvalumab and up to 30 days after last dose of durvalumab.

23. Patients who experience any grade 3-4 gastrointestinal (GI) bleeding within 3 months preceding randomization

24. Diagnosis of sclerosing cholangitis

25. Diagnosis of hepatic encephalopathy

26. Current biliary obstruction requiring surgical diversion or placement of endoscopic or transhepatic stents for biliary decompression

27. Clinically significant ascites (palpable on exam, paracentesis in last 3 months preceding randomization, and/or symptomatic)

28. History of malignant bowel obstruction

29. Subjects with creatinine clearance < 60 mL/min (calculated using the Cockcroft-Gault formula below)

- Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL
- Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL

10.8 Exclusion Criteria 2L Cholangiocarcinoma

30. In the opinion of the investigator, subject has had an incomplete recovery from previous therapy(ies)

31. Concurrent use of immunosuppressive medication, EXCEPT for the following:

a) Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection)

b) Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent

c) Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

32. Patients who experience any grade 3-4 GI bleeding within 3 months preceding randomization

33. Diagnosis of sclerosing cholangitis

34. Diagnosis of hepatic encephalopathy

35. Current biliary obstruction requiring surgical diversion or placement of endoscopic or transhepatic stents for biliary decompression

36. Clinically significant ascites (palpable on exam, paracentesis within 3 months preceding randomization, and/or symptomatic)

37. History of malignant bowel obstruction

38. Subjects with creatinine clearance < 60 mL/min (calculated using the Cockcroft-Gault formula below)

- Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL
- Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL

11. TREATMENT

11.1 Investigational Product

LSTA1 for Injection is a sterile, white, lyophilized powder supplied as 300 mg per vial of LSTA1 acetate for IV administration. LSTA1 Injection consists of LSTA1 drug substance and 0.1% (w/w) EDTA. The pH is adjusted to 5.2-5.4 with NaOH prior to lyophilization.

Excipients used in the formulation are listed in FDA's Inactive Ingredients Database as Generally Regarded as Safe (GRAS) and are United States Pharmacopeia/National Formulary (USP/NF) grade.

11.1.1 Supply Packaging and Labeling

LSTA1 is lyophilized and supplied in single-use, clear Type I glass vials for reconstitution and IV injection. The glass container closure system will consist of 5-mL nominal Type I clear glass vials, lyophilization butyl rubber coated stoppers, and aluminum seals with a flip off cap.

The drug product will be packaged in 5-mL nominal size vials at 300 mg LSTA1 drug substance per vial to be reconstituted with saline according to the Pharmacy Manual.

11.1.2 Storage

The lyophilized LSTA1 should be stored in the freezer at -20°C in a secure, controlled-access location. Storage conditions should be monitored at all times and the sponsor / designee notified of any temperature excursions. The investigational product will be reconstituted and stored according to the Pharmacy Manual Instructions.

11.2 Comparator

A placebo vial will be provided which appears identical with regard to labeling, vial characteristics, and appearance of the lyophilized investigational product cake.

11.3 Chemotherapy

Advanced Head and Neck Squamous Cell Carcinoma:

- Patients in both treatment arms will receive paclitaxel 175 mg/m^2 IV every 21 days.

1L Cholangiocarcinoma:

- Patients in both treatment groups will receive 1500 mg of durvalumab IV, cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 1, and cisplatin 25 mg/m^2 IV and gemcitabine 1000 mg/m^2 IV on day 8 - every 21 days up to 8 cycles. After 8 cycles, both treatment groups will receive 1500 mg of durvalumab IV as monotherapy every 28 days.

2L Cholangiocarcinoma:

- Patients in both treatment groups will receive oxaliplatin 85 mg/m² IV, l-folinic acid 200 mg/m^2 **or** 400 mg/m^2 d,l-folinic acid IV, and fluorouracil (5-FU) 400 mg/m² (IV bolus) on day 1 followed by a continuous 46-hour infusion of 5-FU 2400 mg/m² repeated every 14 days.

No concomitant cytotoxic therapy outside of what is specified in this protocol, whether conventional or investigational, will be allowed during this study.

11.4 Accountability

Site staff must complete drug accountability logs for LSTA1/matching LSTA1 placebo including recording receipt, dispensation, and destruction of the study drug. Drug accountability logs will be included in the Pharmacy Manual.

11.5 Concomitant Medications

Allowed Medications:

Necessary supportive measures for optimal medical care will be given throughout the study according to local institutional practice, including IV antibiotics to treat infections, blood components, anti-emetics, etc. Additional care, including palliative radiotherapy, may be administered as indicated by the treating physician and patient's medical need, and after discussion with the medical monitor.

Per usual standard of care and as clinically indicated, short-term corticosteroids peri-dosing of cytotoxic chemotherapy (i.e., paclitaxel, gemcitabine/cisplatin) is permissible, where the prescribing information for the concomitant cytotoxic agent requires the use of steroids for documented hypersensitivity reactions.

Short-term use of corticosteroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events (e.g., chronic obstructive pulmonary disease exacerbation, radiation, nausea, etc.).

All concomitant medications and supportive therapy administered from screening until 30 days after the last dose of LSTA1/matching LSTA1 placebo must be recorded on the appropriate case report form.

Prohibited Medications:

No other investigational medicinal products will be allowed during this study. Medications or vaccinations specifically prohibited in the exclusion criteria (see Sections 10.4, 10.6, and 10.7) are not allowed during study. If there is a clinical indication for one of these medications or vaccinations specifically prohibited during the study, discontinuation from treatment may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study drug requires the agreement of the investigator, the sponsor, and the subject.

Per the Taxol® (paclitaxel) USPI, the metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4 so caution should be taken with the use of known substrates or inhibitors of CYP2C8 and CYP3A4. Substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine).

Per the cisplatin USPI, caution is advised when administering cisplatin with ototoxic and nephrotoxic drugs.

Warfarin should not be used during this study. Altered coagulation parameters and/or bleeding have been reported in patients receiving chemotherapy agents concomitantly with

anticoagulants such as warfarin. Thus, patients requiring full anti-coagulation before study entry or during the study should be treated with an alternative regimen.

The respective product labels for the components of the FOLFOX regimen should be followed with respect to cautions and contraindications.

11.6 Post-study Anti-cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of study drug. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of study drug, the EOT visit should occur before the first dose of the new anti-cancer therapy.

11.7 Administration of Study Treatments

Study treatments should begin as soon as possible and within 14 days of randomization. Treatment will continue until disease progression or unacceptable toxicity or withdrawal of consent or events leading to permanent discontinuation.

Patients are to receive treatment according to the following schedule, based on the treatment arm allocated within each tumor cohort. In the event of scheduling difficulties, treatment can be given ± 3 days.

Dosing calculations based upon body surface area should be performed as per local treatment guidelines.

Treatment schedule:

Table 2. Treatment Schedule for 2L Head and Neck Squamous Cell Carcinoma

Drug administration sequence	Dose	Route	Infusion duration
Paclitaxel	175 mg/m^2	IV	Administered over 3 hours (± 30 minutes) followed by saline flush
LSTA1 or Placebo	3.2 mg/kg	IV	Administered immediately (within 15 minutes) following paclitaxel administration as slow push over 1 minute (± 30 seconds)

Table 3. Treatment Schedule for 1L Cholangiocarcinoma, First 8 Cycles

Drug administration sequence for first 8 cycles; every 21 days	Dose	Route	Infusion duration	Day 1	Day 8
Durvalumab	1500 mg	IV	Administered over 60 minutes (± 10 minutes) according to USPI or relevant local dosing instructions	X	
Cisplatin	25 mg/m^2	IV	Administered over 30 to 65 minutes followed by saline flush	X	X
LSTA1 or Placebo	3.2 mg/kg	IV	Administered immediately (within 15 minutes) following cisplatin administration as slow push over 1 minute (± 30 seconds)	X	X
Gemcitabine	1000 mg/m^2	IV	Administered over 30 minutes (±5 minutes) starting no more than 10 minutes after completion of LSTA1 or placebo administration	X	X

Table 4. Treatment Schedule for 1L Cholangiocarcinoma, Cycles 9 and Beyond

Drug administration sequence for cycle 9 and beyond; every 28 days	Dose	Route	Infusion duration	Day 1
Durvalumab	1500 mg	IV	Administered over 60 minutes (± 10 minutes) according to USPI or relevant local dosing instructions	X
LSTA1 or Placebo	3.2 mg/kg	IV	Administered immediately (within 15 minutes) following durvalumab and saline flush administration as slow push over 1 minute (± 30 seconds)	X

Table 5. Treatment Schedule for 2L Cholangiocarcinoma

Drug administration sequence: every 14 days	Dose	Route	Infusion duration	Day 1	Day 2-3
Oxaliplatin	85 mg/m²	IV	Administered over 2 hours (± 15 minutes) according to USPI or relevant local dosing instructions	X	
l-folinic acid or d,l-folinic acid	200 mg/m² 400 mg/m²	IV	In separate bag, administered concurrently with oxaliplatin over 2 hours (± 15 minutes) followed by saline flush	X	
Fluorouracil (5-FU)	400 mg/m²	IV bolus	Administered immediately (within 10 minutes) following oxaliplatin/folinic acid infusion, administration as IV bolus over 5 minutes (±5 minutes). Follow 5-FU bolus with saline flush	X	
LSTA1 or Placebo	3.2 mg/kg	IV	Immediately following the 5-FU bolus (within 10 minutes) administered as a slow IV push over 1 minute (± 30 seconds)	X	
Fluorouracil (5-FU)	2400 mg/m²	IV	Administered following LSTA1/placebo slow IV push (within 10 minutes) as continuous infusion (via home-infusion pump) over 46 hours	X	X

11.8 Procedure for Unblinding

Unblinding is not generally necessary for the management of a patient with an adverse event. However, if required, unblinding should be performed using the IRT system.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment assignment. Before unblinding, the investigator should attempt to contact the medical monitor. The investigator documents and

reports the unblinding action as soon as possible but at a minimum within 24 hours to the medical monitor, without revealing the treatment given to the subject.

Sponsor safety staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

11.9 Dose Modifications

In the event the combinations of paclitaxel, durvalumab/cisplatin/gemcitabine, or oxaliplatin/ l-folinic acid or d,l-folinic acid/5-FU treatment is delayed or omitted, LSTA1/matching LSTA1 placebo must also be delayed or omitted on the same day. Once paclitaxel, durvalumab/cisplatin/gemcitabine, or oxaliplatin/ l-folinic acid or d,l-folinic acid/5-FU treatments are restarted, LSTA1/matching LSTA1 placebo must also restart on the same day. There are no prospective provisions for dose reduction of LSTA1/matching LSTA1 placebo in this study.

11.9.1 LSTA1

If ≥3 of the first 10 patients in a specific cohort experience Grade 3 adverse events or ≥2 of the first 10 patients in a specific cohort experience Grade 4 adverse events through the first cycle, which are considered 'possibly, probably, or definitely related' by the investigator to study drug, the sponsor will perform a blinded review of these events in an effort to confirm the relationship to study drug (i.e., assess the temporal relationship, biologic plausibility, dechallenge). Should the relationship to study drug be confirmed, enrollment and dosing in the 3.2 mg/kg dose will stop in the specific cohort and enrollment and dosing will thereafter commence in that cohort with a reduced dose of LSTA1 at 1.6 mg/kg.

11.9.2 Dose Interruption or Reduction for Chemo/Immunotherapeutic Agents

In managing toxicities, every effort should be made to provide maximal supportive therapy prior to implementing a dose reduction. Patients should be educated on the common toxicities associated with study agents and how they may be managed.

11.9.2.1 2L Head and Neck Squamous Cell Carcinoma Cohort

Recommendations for dose interruptions and reductions for patients receiving paclitaxel are outlined below. Dosing changes for paclitaxel that are not defined here can be done as clinically warranted, in agreement between the Investigator and the Sponsor.

Paclitaxel dose reduction levels are defined in Table 6 below.

Table 6. Dose Level Reduction Definitions for Paclitaxel

Dose Level	Paclitaxel (mg/m^2)
Full dose	175
1st dose reduction	135
2nd dose reduction	100
If additional dose reduction required	Discontinue

Dose level modifications and reductions are provided in Table 7, Table 8, and Table 9.

Table 7 describes the dose modifications for neutropenia and thrombocytopenia. Table 8 outlines the dose modifications from adverse drug reactions. Table 9 describes dose recommendations for patients with hepatic impairment. The referenced dose reduction levels are in Table 6.

Table 7. Paclitaxel dose recommendation and modifications for neutropenia and/or thrombocytopenia at the start of a cycle or within a cycle

Cycle day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	Paclitaxel
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	≥ 500 to < 1000	OR	≥ 50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses

Table 8. Paclitaxel dose modifications for other adverse drug reactions

Adverse Drug Reaction	Paclitaxel	
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction*
Cutaneous Toxicity Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

Table 9. Recommendations for paclitaxel dosing in patients with hepatic impairment based on clinical trial data

Degree of Hepatic Impairment			Recommended[a] TAXOL Dose[c]
Transaminase Levels		Bilirubin Levels[b]	
24-hour infusion			
<2 x ULN	and	≤1.5 mg/dL	135 mg/m^2
2 to <10 x ULN	and	≤1.5 mg/dL	100 mg/m^2
<10 x ULN	and	1.6–7.5 mg/dL	50 mg/m^2
≥10 x ULN	or	>7.5 mg/dL	Not recommended
3-hour infusion			
<10 x ULN	and	≤1.25 x ULN	175 mg/m^2
<10 x ULN	and	1.26–2.0 x ULN	135 mg/m^2
<10 x ULN	and	2.01–5.0 x ULN	90 mg/m^2
≥10 x ULN	or	>5.0 x ULN	Not recommended

a These recommendations are based on dosages for patients without hepatic impairment of 135 mg/m^2 over 24 hours or 175 mg/m^2 over 3 hours; data are not available to make dose adjustment recommendations for other regimens (e.g., for AIDS-related Kaposi's sarcoma).

b Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design.

c Dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance.

Sepsis: Sepsis has occurred in patients with or without neutropenia (risk factors are biliary obstruction or presence of a biliary stent). Initiate broad spectrum antibiotics in the presence of fever, even if not neutropenic. Interrupt paclitaxel until sepsis resolves and, if neutropenic, until neutrophils are at least 1500 cells/mm3 then resume at lower doses.

Hepatotoxicity: Paclitaxel is not recommended for individuals with preexisting moderate to severe hepatic impairment; the need for further dose adjustments because of hepatotoxicity in subsequent courses should be based on individual tolerance and clinician judgment.

11.9.2.2 1L Cholangiocarcinoma Cohort

Recommendations for dose interruptions and reductions for patients receiving cisplatin and gemcitabine are outlined below.[‡‡] Dosing changes for cisplatin and gemcitabine that are not defined here can be performed as clinically warranted, in agreement between the Investigator and the Sponsor.

‡‡ Systemic Anti Cancer Treatment Protocol. Gemcitabine-Cisplatin. https://www.clatterbridgecc.nhs.uk/application/files/6515/2759/3109/Gemcitabine-Cisplatin_Protocol_V1.0.pdf and CISPLATIN and GEMCITABINE for biliary tract cancers. Drug Administration Schedule. https://www.northerncanceralliance.nhs.uk/wp-content/uploads/2018/11/CISPLATIN-GEMCITABINE-protocol-CRP09-UGI008-v1.5.pdf

Cisplatin/Gemcitabine Hematologic toxicity:

Consider blood transfusion if the patient is symptomatic of anemia or hemoglobin less than 12g/dL.

Any subsequent day of chemotherapy treatment if the neutrophil count is between $0.5x10^9$ /L and $1x10^9$ /L and / or the platelet count is between $50x10^9$ /L and $75x10^9$ /L administer 75% of the original dose for both cisplatin and gemcitabine. Reduce the dose of cisplatin and gemcitabine to 50% of the original dose if the neutrophil count is less than $0.5x10^9$ /L and / or the platelet count less than $50x10^9$ /L. Consider stopping treatment after a second dose reduction or interruption due to hematological toxicity.

Table 10. Cisplatin/Gemcitabine Organ Impairment

Hepatic Impairment	Bilirubin	AST/ALT	Dose (% of original dose)
Cisplatin	No dose reductions necessary		
Gemcitabine	Consider dose reductions especially if bilirubin is elevated		
Renal Impairment			
Cisplatin	>60	100	
	45-59	75	
	Less than 45	Consider discontinuing	
Gemcitabine	Consider dose adjustments when the CrCl is less than 30 mL/min		

Non-hematological cisplatin/gemcitabine toxicities:

For patients with grade 3 non-hematological toxicities (excluding nephrotoxicity), reduce the dose to 75% of the original dose and 50% of the original dose for grade 4 non-hematological toxicities.

Durvalumab dosage modification:

In general, withhold durvalumab for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue durvalumab for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Dose modifications for adverse reactions that require management different from the aforementioned guidelines are summarized below in Table 11.[§§]

[§§] IMFINZI – durvalumab injection, solution. U.S. Package Insert.
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8baba4ea-2855-42fa-9bd9-5a7548d4cec3

Table 11. Recommended Durvalumab Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Immune-Mediated Adverse Reactions		
Pneumonitis	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver‡	ALT or AST increases to more than 3 and up to 8 times the ULN or total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold†
	ALT or AST increases to more than 8 times ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver‡	AST or ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times ULN or AST or ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times ULN	Withhold†
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold†
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold†
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

* Based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

† Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

‡ If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement.

11.9.2.3 2L Cholangiocarcinoma Cohort

Patients should be observed closely for platinum hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of oxaliplatin. Facilities for the treatment of hypotension and bronchospasm must be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require discontinuation of therapy: the infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. An anti-histamine may be administered. Severe reactions, such as hypotension, bronchospasm or generalized rash/erythema require immediate discontinuation of oxaliplatin, and appropriate therapy should be initiated. Oxaliplatin may cause transient paresthesia of hands and feet and laryngopharyngeal dysesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patients should be well advised on precautions to be taken. This does not require treatment or dose reduction, but subsequent infusions should be given over 6 hours.

Hematologic toxicity:

- Defer treatment for 1 week if neutrophil count < 1.0 x 10^9/L or platelets < 75 x 10^9/L.
- If platelets 10-49 x 10^9 /L defer until ≥ 75 x 10^9 /L and reduce oxaliplatin dose to 65 mg/m^2 (if second occurrence reduce oxaliplatin dose to 55mg/ m^2).
- If platelets < 10 x 10^9 /L defer until ≥ 75 x 10^9 /L and reduce oxaliplatin dose to 55 mg/m^2 (if second occurrence – discuss with Sponsor).
- If febrile neutropenia (neutrophils < 0.5 x 10^9/L and fever requiring IV antibiotics) – reduce all subsequent doses of fluorouracil to 50% and oxaliplatin dose to 55 mg/m^2.
- If after resuming treatment, neutrophil count drops to less than 1 x 10^9/L for a second time, the bolus dose of 5-fluorouracil may be dropped from the regimen after discussion with the Sponsor.

Table 12. Recommended Dose Adjustments for Renal Impairment

CrCl (mL/min)	Oxaliplatin dose	Fluorouracil dose
≥ 50	100%	100%
30-49	50%	100%
10-29	Omit	100%
< 10	Omit	Consider dose reduction

Table 13. Recommended Dose Adjustments for Hepatic Impairment

Bilirubin (x ULN)		AST/ALT (x ULN)	Oxaliplatin dose	Fluorouracil dose
≤ 1.5	and	≤ 1.5	100%	100%
1.5 – 3	and	≤ 3	100%	Consider dose reduction
3 – 5	or	3 – 5	50%	Consider dose reduction
>5	or	>5	Omit	Contraindicated

Table 14. Recommended Dose Adjustments for Other Toxicities

Toxicity	Definition	Oxaliplatin dose	Fluorouracil dose
Diarrhea*	Grade 2	100%	80%
	Grade 3	65 mg/m^2	50%
	Grade 4	Discontinue Treatment	
Stomatitis/Mucositis	Grade 2	100%	80%
	Grade 3	65 mg/m^2	50%
	Grade 4	Discontinue Treatment	
Palmar-Plantar erythema	Grade 2	100%	80%
	Grades 3/4	100%	50%
Peripheral neuropathy	Grade 2/3	65 mg/m^2	100%
	Grade 4	Discontinue	100%

*Patients presenting with diarrhea must be carefully monitored until the symptoms have disappeared completely, since a rapid (sometimes fatal) deterioration can occur. For diarrhea ≥ grade 3, consider treating with antibiotics.

- Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhea and/or severe stomatitis early in the first cycle). Avoid use in patients with known DPD deficiency.
- Cardiotoxicity has been associated with fluoropyrimidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias, or angina pectoris.
- Dose related peripheral sensory neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800 mg/m^2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

11.10 Adherence

Patients and study sites are encouraged to maintain appropriate treatment with the study intervention without interruption. When treatment is missed or discontinued for any reason, relevant information should be documented within the electronic case report form (eCRF).

12. TUMOR RESPONSES

Radiological assessment of tumor will be repeated every 8 weeks. Tumor assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the C1D1 date.

Response rate (RR): defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[25,***] For this study, measurable disease will be defined as the presence of at least one measurable lesion. Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: 10 mm by CT or MRI scan (the scan slice thickness no greater than 5 mm, when the scans have slice thickness > 5 mm, the minimum size should be twice the slice thickness); 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable). For a lymph node to be considered measurable, it should be at least 15 mm in the short diameter.

Complete Response (CR): defined as complete disappearance of all target lesions, confirmed by repeat assessments at no less than 4 weeks after the criteria for response are first met.

Partial Response (PR): defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the longest diameters.

Progressive Disease (PD): defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this may be the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameter since the treatment started.

Duration of response (DOR): defined as time from first observation of an objective response which is subsequently confirmed, to first disease progression. DOR is censored if the patient dies from a non-cancer cause.

12.1 Tumor Imaging

Imaging of the relevant body part(s) is required either by CT scan with contrast or MRI, whichever is appropriate for the patient's tumor. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

*** https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

12.1.1 Tumor Imaging During Screening

Initial tumor imaging must be performed within 28 days before the first dose of study drug. The site study team must review pre-study images to confirm that the subject has measurable disease per RECIST v1.1. Additionally, it is recommended that tumor lesions selected for biopsy not be selected as target lesions for RECIST measurement.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study drug.

12.1.2 Tumor Imaging During the Study

The first imaging assessment should be performed 8 weeks after C1D1 and then every 8 weeks (56 days ± 7 days) for 12 months and then every 12 weeks (± 7 days) thereafter until disease progression is determined. Imaging assessments may be done more frequently if clinically indicated. Imaging should not be delayed for delays in cycle starts.

Imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. A central imaging vendor will not be used in this study.

12.1.3 Tumor Imaging During Follow-Up

If the subject discontinues study drug for reasons other than disease progression, imaging assessments should continue at the protocol-specified interval until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

If a scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation (EOT) is not mandatory. For subjects who discontinue study drug without confirmed disease progression, a radiologic evaluation should be repeated at the time of treatment discontinuation (i.e., date of discontinuation ± 4-week window).

12.2 Repeat Imaging to Confirm Progressive Disease for 1L Cholangiocarcinoma

If radiologic imaging shows progressive disease in subjects with 1L cholangiocarcinoma, then tumor assessments should be repeated at a minimum of 4 weeks, but no later than 6 weeks later to confirm progression, with the option of continuing treatment while awaiting radiologic confirmation of progression. Table 15 provides instructions on how to proceed with treatment based on the subject's clinical status once the initial scan showing radiologic evidence of progression is observed.

Subjects may receive treatment while waiting for confirmation of progression if they are clinically stable as defined by the following criteria:

- Absence of clinically significant signs and symptoms (including worsening of laboratory findings) consistent with disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomic sites (such as spinal cord compression) requiring urgent alternative medical intervention

Table 15. Imaging and Treatment After First Radiographic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Tumor Imaging	**Treatment**	**Tumor Imaging**	**Treatment**
First radiologic evidence of progression	Repeat imaging 4-6 weeks to confirm progression	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging	Repeat tumor imaging 4-6 weeks to confirm progression per physician discretion only	Discontinue treatment
Repeat scan confirms progression	No additional tumor imaging required	Discontinue treatment	No additional tumor imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled tumor imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled tumor imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

As noted above, if disease progression is observed, then the study site may elect to continue treatment, repeat imaging at a minimum of 4 weeks, but no later than 6 weeks later, and assess tumor response or confirmed progression per RECIST.

In determining whether or not the tumor burden has increased or decreased, study site investigators should consider all target lesions as well as nontarget lesions. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation. If radiologic progression is confirmed by subsequent scan, then the subject should be discontinued from study treatment. If radiologic progression is not confirmed, then the subject should resume or continue study treatment and have the next tumor imaging according to the protocol schedule. If progression is not confirmed and the subject continues on treatment, then the date of the next scan that documents disease progression (and is confirmed by a second

scan at least 4 weeks, but no later than 6 weeks later) will be considered the date of disease progression.

If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks, but no later than 6 weeks apart demonstrating progression) per RECIST, but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered after consultation with the medical monitor. Clinically stable subjects at the confirmatory scan should also have no further increase in the target lesions, no unequivocal increase in nontarget lesions, and no additional new lesions develop (non-worsening disease progression) to continue study treatment.

13. PHARMACOKINETIC ASSESSMENTS

The sample collection for the plasma PK analysis for LSTA1 will be performed at the specified times described in Table 16.

. Blood samples (~ 4 mL) are to be collected as follows:

- Samples should be taken from a peripheral vein whenever possible.
- Samples should be taken from the contralateral arm of any concomitant chemotherapy or LSTA1 that is being infused in a peripheral vein.
- If peripheral vein access is not possible, samples may be drawn from a central line via the method outlined in the laboratory manual.

The actual time of blood collection must be documented in the respective form and any deviations outside of the time limits must be commented upon. The scheduled blood sampling times will be used for the PK analysis; however, any deviations outside the limits (actual times) are relevant and the data sets will be adjusted for the PK evaluations and the actual times will be used. A Laboratory Manual will be provided with instructions for collecting, processing, and shipping the samples to the central laboratory.

Plasma concentration will be used to determine the following PK parameters:

- AUC_{0-t} Area under the concentration time curve from time zero to last observation
- $AUC_{0-\infty}$ Area under the concentration time curve from time zero to infinity
- C_{max} Maximum plasma concentration
- T_{max} Time to maximum plasma concentration
- $t_{1/2}$ Terminal phase half life
- CL/F Total body clearance
- V_d/F Apparent volume of distribution

Table 16. Pharmacokinetic Sampling Times

Cycle	Day	Sample	Collection Times[1]
Run-in	1	1	30 minutes post-dose (± 15 min)
1	1	1	Pre-dose[2]
		2	3 minutes post-dose (± 1 min)
		3	15 minutes post-dose (± 3 min)
		4	30 minutes post-dose (± 3 min)
		5	1 hour post-dose (± 5 min)
		6	3 hours post-dose (± 10 min)
		7	6 hours post-dose (± 10 min)
2	1	1	30 minutes post-dose (± 15 min)
3	1	1	30 minutes post-dose (± 15 min)
4	1	1	30 minutes post-dose (± 15 min)
5	1	1	30 minutes post-dose (± 15 min)
6	1	1	Pre-dose[2]
		2	3 minutes post-dose (± 1 min)
		3	15 minutes post-dose (± 3 min)
		4	30 minutes post-dose (± 3 min)
		5	1 hour post-dose (± 5 min)
		6	3 hours post-dose (± 10 min)
		7	6 hours post-dose (± 10 min)

[1] Times are calculated from the completion of LSTA1 infusion.
[2] Within 60 minutes before LSTA1 infusion

14. PHARMACODYNAMIC ASSESSMENTS

The following pharmacodynamic assessments will be performed:

- For both CCA cohorts, disease biomarkers CA19-9, CEA, and CA125 will be assessed pre-dose (within 72 hours prior to dosing) at run-in and on Day 1 of each Cycle and at EOT using local laboratories.
- For all cohorts, retrospective assessment of tissue biomarkers in optional pre-treatment biopsy archival tissue (or pre-treatment core biopsy) and post-treatment optional core biopsy will be assessed. Optional archival and post-treatment core biopsy tissue samples may be evaluated to assess exploratory pharmacodynamic biomarkers. These will be collected according to institutional SoC and processed as per the instructions provided in the Laboratory Manual.

15. STUDY VISIT ASSESSMENTS

15.1 Screening for All Subjects

The following should occur within 28 days prior to randomization unless otherwise indicated:

- Review inclusion and exclusion criteria to confirm study eligibility
- Sign informed consent
- Collect medical history including history of cancer (histological diagnosis, pathological classification, clinical staging, genetic mutation results (if applicable), and treatment history), previous major medical history (e.g., diabetes, cardiovascular disease, major chronic diseases and corresponding treatments, previous surgical history (e.g., diagnostic, or therapeutic invasive surgery)
- Obtain archival core biopsy tissue (if available) or fresh core biopsy tissue if archival tissue is unavailable (optional)
- Collect information on concomitant medications (including non-drug therapies)
- Perform a complete physical examination including height and weight assessment
- Perform a vital sign assessment including temperature, blood pressure, pulse rate, and respiratory rate
- Perform 12-lead ECG
- Assess ECOG status
- Assess combined positive score (CPS) score
- Perform urine or serum pregnancy test on women of childbearing potential (WOCBP)
- Collect blood for clinical chemistry including sodium (Na), potassium (K), chloride (Cl), magnesium (Mg), calcium (Ca), bicarbonate (HCO_3)/carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, total protein, total bilirubin, glucose, and lactate dehydrogenase (LDH)
- Collect blood for hematology including hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets
- Collect blood for coagulation parameters including prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)
- Perform imaging of relevant body parts (e.g., head and neck, chest, abdomen, and pelvis) to assess tumor burden
- Assess for adverse events

15.2 Randomization and Run-in Period for All Subjects

15.2.1 Run-in Day 1

Once eligibility is confirmed, subjects will be randomized in the IRT system within their respective tumor type basket arm 1:1 to one of the two treatment groups (i.e., SoC + placebo vs. SoC + LSTA1).

The following will occur during the 72-hour run-in:

- Perform a targeted physical examination (does not need to be completed if performed less than 72 hours before randomization) including weight assessment within 24 hours of dosing
- Perform a vital sign assessment pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
- Perform 12-lead ECG 15 minutes (± 5 minutes) after IP administration
- Collect blood for CA19-9, CEA, and CA125 within 72 hours of dosing (CCA cohorts only)
- Perform urine or serum pregnancy test on WOCBP within 24 hours prior to administration of study drug
- Administer LSTA1 or LSTA1 matching placebo
- Assess for adverse events
- Collect PK blood sample as outlined in Section 13

15.3 During Treatment Head and Neck Squamous Cell Carcinoma

15.3.1 Day 1 of Cycle 1 of treatment (HNSCC)

The following will be performed or assessed:

- Perform a targeted physical examination (within 24 hours prior to dosing)
- Weight assessment within 24 hours of dosing
- Collect information on concomitant medications (including non-drug therapies)
- Perform a vital sign assessment pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
- Perform 12-lead ECG 15 minutes (± 5 minutes) after IP administration

- Assess ECOG performance status within 24 hours of dosing
- Perform urine or serum pregnancy test on WOCBP within 24 hours prior to administration of study drug
- Collect blood for clinical chemistry including Na, K, Cl, Mg, Ca, bicarbonate/carbon dioxide, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH within 72 hours of dosing
- Collect blood for hematology including hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets within 72 hours of dosing
- Assess for adverse events
- Collect PK blood samples as outlined in Section 12
- Administer LSTA1 or LSTA1 matching placebo
- Administer paclitaxel

15.3.2 Day 1 of each subsequent cycle every 21 Days (± 3 Days) (HNSCC)

The following will be performed or assessed:

- Perform a targeted physical examination (within 24 hours prior to dosing)
- Weight assessment within 24 hours of dosing
- Collect information on concomitant medications (including non-drug therapies)
- Perform a vital sign assessment pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
- Assess for adverse events
- Perform 12-lead ECG 15 minutes (± 5 minutes) after IP administration (only for Cycles 3 and 6)
- Assess ECOG performance status within 24 hours of dosing
- Perform urine or serum pregnancy test on WOCBP within 24 hours prior to administration of study drug
- Collect blood for clinical chemistry including Na, K, Cl, Mg, Ca, bicarbonate/carbon dioxide, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH within 72 hours of dosing

- Collect blood for hematology including hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets within 72 hours of dosing
- Assess tumor burden every 8 weeks (± 7 days) using the same radiological evaluation used at screening
- Collect PK blood samples as outlined in Section 12 (through Cycle 6)
- Administer LSTA1 or LSTA1 matching placebo
- Administer paclitaxel

15.4 During Treatment of 1L Cholangiocarcinoma (1L-CCA)

15.4.1 Day 1 of the first 8 Cycles (every 21 Days ± 3 Days) of treatment (1L-CCA)

The following will be performed or assessed:

- Perform a targeted physical examination (within 24 hours prior to dosing)
- Weight assessment within 24 hours of dosing
- Collect information on concomitant medications (including non-drug therapies)
- Perform a vital sign assessment pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
- Perform 12-lead ECG 15 minutes (± 5 minutes) after IP administration (only for cycles 1, 3, and 6)
- Assess ECOG performance status within 24 hours of dosing
- Perform urine or serum pregnancy test on WOCBP within 24 hours prior to administration of study drug
- Collect blood for clinical chemistry including Na, K, Cl, Mg, Ca, bicarbonate/carbon dioxide, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH within 72 hours of dosing
- Collect blood for hematology including hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets within 72 hours of dosing
- Assess tumor burden every 8 weeks (± 7 days) using the same radiological evaluation used at screening

- Collect serum CA19-9, CEA, and CA125 biomarkers within 72 hours of dosing
- Assess for adverse events
- Collect PK blood samples as outlined in Section 13 (through Cycle 6)
- Administer LSTA1 or LSTA1 matching placebo
- Administer durvalumab, cisplatin, and gemcitabine

15.4.2 Days 8 (± 1 Day) of the first 8 Cycles of treatment (1L-CCA)

The following will be performed or assessed:

- Collect information on concomitant medications (including non-drug therapies)
- Perform a targeted physical examination (within 24 hours prior to dosing)
- Weight assessment within 24 hours of dosing
- Perform a vital sign assessment pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
- Assess ECOG performance status within 24 hours of dosing
- Perform urine or serum pregnancy test on WOCBP within 24 hours prior to administration of study drug
- Collect blood for hematology including hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets within 72 hours of dosing
- Assess for adverse events
- Administer LSTA1 or LSTA1 matching placebo
- Administer cisplatin and gemcitabine

15.4.3 Day 1 Cycles 9 and beyond (every 28 Days ± 3 Days)

The following will be performed or assessed:

- Perform a targeted physical examination (within 24 hours prior to dosing)
- Weight assessment within 24 hours of dosing
- Collect information on concomitant medications (including non-drug therapies)

- Perform a vital sign assessment pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
- Assess ECOG performance status within 24 hours of dosing
- Perform urine or serum pregnancy test on WOCBP within 24 hours prior to administration of study drug
- Collect blood for clinical chemistry including Na, K, Cl, Mg, Ca, bicarbonate/carbon dioxide, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH within 72 hours of dosing
- Collect blood for hematology including hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets within 72 hours of dosing
- Collect blood for CA19-9, CEA, and CA125 biomarkers within 72 hours of dosing
- Assess tumor burden every 8 weeks (± 7 days) using the same radiological evaluation used at screening
- Assess for adverse events
- Administer LSTA1 or LSTA1 matching placebo
- Administer durvalumab

15.5 During Treatment of 2L Cholangiocarcinoma (2L-CCA)

15.5.1 Day 1 for (every 14 Days ± 3 Days) of treatment

The following will be performed or assessed:

- Perform a targeted physical examination (within 24 hours prior to dosing)
- Weight assessment within 24 hours of dosing
- Collect information on concomitant medications (including non-drug therapies)
- Perform a vital sign assessment pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) including temperature, blood pressure, pulse rate, and respiratory rate
- Perform 12-lead ECG 15 minutes (± 5 minutes) after IP administration (only for cycles 1, 3, and 6)
- Assess ECOG performance status within 24 hours of dosing

- Perform urine or serum pregnancy test on WOCBP within 24 hours prior to administration of study drug
- Collect blood for clinical chemistry including Na, K, Cl, Mg, Ca, bicarbonate/carbon dioxide, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH within 72 hours of dosing
- Collect blood for hematology including hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets within 72 hours of dosing
- Assess tumor burden every 8 weeks (± 7 days) using the same radiological evaluation used at screening
- Collect serum CA19-9, CEA, and CA125 biomarkers within 72 hours of dosing
- Assess for adverse events
- Collect PK blood samples as outlined in Section 13 (through Cycle 6)
- Administer LSTA1 or LSTA1 matching placebo
- Administer oxaliplatin, folinic acid, and 5-FU

15.6 End of Treatment Visit 30 Days (± 7 Days) after last dose of study treatment for all subjects

The following will be performed or assessed:

- Obtain fresh core biopsy tissue (optional)
- Perform a targeted physical examination including weight assessment
- Perform a vital sign assessment including temperature, blood pressure, pulse rate, and respiratory rate
- Collect information on concomitant medications (including non-drug therapies)
- Assess for adverse events
- Assess ECOG performance status
- Perform urine or serum pregnancy test on WOCBP
- Collect blood for clinical chemistry including Na, K, Cl, Mg, Ca, bicarbonate/carbon dioxide, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH

- Collect blood for hematology including hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets
- Collect blood for CA19-9, CEA, and CA125 (CCA cohort only)
- Assess tumor burden using the same radiological evaluation used at screening

15.7 Follow-up every 12 weeks (± 4 weeks) after EOT visit for all subjects

The follow-up visit may be conducted by telephone or based upon record review. The following will be assessed:

- Assess for vital status (survival)
- Record subsequent chemotherapy treatments, if applicable

16. SUBJECT MANAGEMENT

16.1 Informed Consent and Enrollment

Subjects will be enrolled when they have provided informed consent (i.e., signs and dates the informed consent form to participate in the study), met all inclusion and none of the exclusion criteria, and completed the screening period.

Subjects who have failed the screening process will be recorded as a screen failure. The study site is responsible for maintaining a screening/enrollment log that includes all subjects evaluated for inclusion in the study. The log also will serve to document the reason for screening failure. All screening data will be collected and reported, regardless of screening outcome.

16.2 Subject Numbering

All subjects will sign an ICF and be assigned a unique 6-digit subject number by the IRT system.

16.3 Randomization and Blinding

Randomization within each tumor type cohort will occur via the IRT system. Randomization must not occur until eligibility has been confirmed by the investigator. Once randomization is completed, the patient will be assigned to a study arm.

The randomization will be stratified by the following stratum:

- ECOG performance status

This is a double-blind study. Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the investigators from the IRT system when

needed. Routines for this will be described in the IRT user manual that will be provided to each site.

16.4 Number of Subjects

Approximately 83 evaluable subjects may be enrolled in this study (at least 40 per CCA cohort and 3 from the discontinued HNSCC cohort).

16.5 Withdrawal of Subjects from Study Drug

Reasons for discontinuation will be reported, including screen failure, adverse event (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], withdrawal of consent), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by Sponsor, or other (reason to be specified by the investigator, e.g., technical problems).

For any subject discontinuation or withdrawal, an attempt will be made to obtain follow-up data, per protocol, through the intended completion of the study, if possible.

16.5.1 Patient Discontinuation

Individual patients may be discontinued from treatment by the Investigator or the Sponsor at any time for reasons outlined below. Patients may voluntarily withdraw at any time. The Investigator will provide a written report on the appropriate eCRF page describing the reason for discontinuation. If a patient withdraws or is discontinued from treatment, every effort should be made to complete EOT visit assessments as outlined in Section 15.4, and to monitor the patient for AEs for 30 days after the last dose of study drug or until resolution of AEs, whichever comes first. The data should be documented on the appropriate eCRF page.

16.5.1.1 Adverse event

If a patient suffers an AE that, in the judgment of the Investigator or the Sponsor, presents an unacceptable consequence or risk to the patient, the patient may be discontinued from further treatment in the study.

16.5.1.2 Intercurrent illness

A patient may also be discontinued from treatment if, in the judgment of the Investigator, he or she develops an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies his withdrawal from the study.

16.5.1.3 Progressive disease

A patient will be discontinued from treatment if he or she develops progressive disease either as documented per RECIST criteria v 1.1 or as clinical progression in the opinion of the investigator.

16.5.1.4 Pregnancy

A patient will be discontinued from treatment if she becomes pregnant.

16.5.1.5 Administrative discontinuation

After consultation between the Investigator and the Sponsor, when appropriate, a patient may be discontinued from treatment for the following administrative reasons:

- Noncompliance
  - Failure to receive study drug
  - Failure to comply with protocol requirements
  - All occurrences of noncompliance must be documented on the appropriate eCRF pages.

- Refusal of study drug administration
  - If, for any reason, the patient refuses study drug administration during the study, the patient will be discontinued from the study, and the reasons for refusal will be documented on the appropriate eCRF page.

- Sponsor/Institutional Review Board (IRB)/Regulatory Authority termination or suspension of the study

16.5.2 Stopping of the Study or Study Site Termination

If an Investigator, the Sponsor, or appropriate regulatory authority discover conditions arising during the study that indicate that the study should be halted or that the study site should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, and Medical Monitor. Conditions that may warrant termination of the study or discontinuation of a study site include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study

- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product

- Failure of the Investigator to enroll patients into the study at a rate commensurate with good clinical research practice and acceptable to the Sponsor

- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities

- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority

- Insufficient adherence to protocol requirements

Study termination and follow up will be performed in compliance with the conditions set forth in the International Council on Harmonization Guidance on Good Clinical Practice ICH E6(R2), with appropriate notification of all IRBs.

Study sites will be considered closed once all study-related activities are completed and the study essential documents are ready for archiving.

16.6 End of Study

A subject's participation in study follow-up will end for any of the following reasons:

- Subject is known to have died
- Consent is withdrawn for any further contact to this study (Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded)
- Sponsor/IRB/Regulatory Authority termination or suspension of the study
- Subject is lost to follow-up

17. ASSESSMENT OF SAFETY

All scheduled assessments must be performed relative to the start of the dosing cycle such that laboratory procedures, etc., required for dosing should be performed according to the schedule of assessments.

17.1 Medical History, Concomitant Medications, and Non-Drug Therapy History

At screening, the subject's medical history will be collected for the following body systems (including past surgeries and start and end dates), if known eyes, ears, nose, mouth, and throat; respiratory; cardiovascular; GI; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary. Additionally, the subject's history of cancer including histological diagnosis, pathological classification, clinical staging, genetic mutation results (if applicable), CPS score (if available), and treatment history will be collected.

Beginning from the time of consent, all medications taken, and non-drug therapies received, and all concomitant medications taken or administered during the study will be documented in the subject's study records.

17.2 Physical Examinations

At screening and subsequent study visits, a physical examination will be performed. A complete physical exam assessment includes general appearance, head and neck, eyes, ears,

nose, mouth, and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological assessment. Targeted physical examinations, per the Schedule of Assessments, will be symptom-directed. The physical examinations should be performed by the same investigator each time, whenever possible. If an abnormal condition is detected at screening, the condition will be described on the medical history form. At subsequent study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE form.

Height (cm) will be collected only at the screening visit, and weight (kg) will be collected at screening, pre-dose, and at EOT.

17.3 ECOG Performance Status

ECOG performance status should be assessed per Table 17.

Table 17. ECOG Performance Status

Grade	Eastern Cooperative Oncology Group (ECOG)
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

17.4 Clinical Laboratory Parameters

All laboratory assessments below must be performed and analyzed locally.

17.4.1 Hematology

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils), and platelet count. Hematology can be evaluated in either the fed or fasted state.

17.4.2 Clinical Chemistry

The clinical chemistry panel will consist of electrolytes (Na, K, Cl, Mg, Ca), bicarbonate/carbon dioxide, BUN, creatinine, AST, ALT, ALP, albumin, total protein, total bilirubin, glucose, and LDH. Clinical chemistry can be evaluated in the fed or fasted state.

17.4.3 Coagulation Parameters

The coagulation parameters will consist of PT (sec), aPTT (sec), and INR.

17.4.4 Pregnancy Testing

Urine or serum pregnancy testing for human chorionic gonadotrophin (hCG) will be performed on WOCBP at the screening visit, repeated within 24 hours prior to first dose of study drug, within 24 hours prior to administration of study drug, and at EOT.

17.5 Vital Signs

Vital signs should be assessed pre-dose (0–120 minutes prior) and post-dose (within 15 minutes) on all dosing days. Vital signs will include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mm Hg). Blood pressure should be measured in the sitting position after 5 minutes of rest.

Vital sign values are to be recorded. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 17.6). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign will be recorded on the AE form. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

17.6 Adverse Events

All AEs will be recorded from signing the informed consent until 30 days after treatment discontinuation. An AE is defined as any untoward medical occurrence in a subject administered IP, regardless of a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP. An AE includes any event, regardless of the presumed causality between the event and the IP.

Any subject experiencing an AE will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically necessary for the safety and well-being of the subject. The subject will remain under observation if medically indicated in the opinion of the investigator.

AEs that occur prior to treatment will be considered non-treatment emergent AEs. AEs that occur during or after treatment will be considered treatment emergent AEs. Treatment emergent AEs will be analyzed separately. All AEs will be described using the sign, symptom, or medical diagnosis on the AE form in standard medical terminology to avoid the use of vague, ambiguous, or colloquial expressions.

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (NCI CTCAE Grade 1 to 5) as described in Section 17.6.6
- Causal relationship to administration procedure, paclitaxel, cisplatin/gemcitabine, durvalumab, and LSTA1 as defined in Section 17.6.7
- The start and end dates, unless unresolved at final follow-up
- The action taken with regard to study drug
- The event outcome (e.g., not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
- The seriousness, as per SAE definition provided in Section 17.6.1

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 17.6.8).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the AE form in the eCRF and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until resolution, medically stabilized, or 30 days after the patient's termination visit, whichever comes first, or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (e.g., between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

17.6.1 Serious Adverse Event

An adverse event is considered serious if, in the view of either the investigator or the Sponsor, it results in at least one of the following criteria:

- Outcome is fatal/results in death
- Is life-threatening (at the time of the event)
- Requires hospitalization or results in prolongation of an existing hospitalization, unless the hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions
- Constitutes a congenital anomaly/birth defect
- Is a medically important event – that may not be immediately life-threatening or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above (e.g., infection, allergic reaction, etc.)

Symptoms and clinical manifestations of disease progression can be classified as an SAE (if it meets the above criteria), however, progressive disease is not an SAE.

Each SAE will be followed until resolution, medically stabilized, or 30 days after EOT visit, whichever comes first. All SAEs are to be reported to the Sponsor within 24 hours of becoming aware of the event.

17.6.2 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of a SAE.

17.6.3 Laboratory Abnormalities

For this study, all Grade 3 and 4 non-hematologic laboratory toxicities and hematologic laboratory toxicities will be listed as AEs. To the extent possible, all laboratory abnormalities observed during the study will be included under a reported AE describing a clinical syndrome (e.g., elevated blood urea nitrogen and creatinine in the setting of an AE of "renal failure" or elevated ALT/AST in the setting of an AE of "hepatitis"). In these cases (e.g., an AE of renal failure), the laboratory abnormality itself (e.g., elevated creatinine) does not need to be recorded as an AE.

In the absence of a reported AE identifying a clinical syndrome that encompasses the observed laboratory abnormality, the "isolated" laboratory abnormality itself should be reported as an AE. The criteria for "clinically significant" laboratory abnormalities include a laboratory abnormality that is judged to be associated with study drug administration and resulting in dose reduction, suspension, or discontinuation or a laboratory abnormality that results in any treatment-emergent therapeutic intervention (i.e., concomitant medication or therapy), or any other laboratory abnormality judged by the investigator to be of other particular clinical relevance.

Patients experiencing AEs or laboratory abnormalities should be assessed and appropriate evaluations performed until all parameters have returned to baseline levels or are consistent with the patient's then-current physical condition.

17.6.4 Medical Conditions which should not be reported as AEs/SAEs

Preexisting diseases that are present before entry into the study (as described in the medical history) will not be recorded as AEs but will be documented in the subject's initial history. Preexisting diseases that manifest with the same severity, frequency, or duration after IP exposure also will not be recorded as AEs but will be documented in the subject's initial history. However, when there is an increase in the severity or duration of a preexisting disease, the event must be described as an AE, and recorded on the form.

Progression of the underlying disease might be reasonably anticipated given the nature and severity of the underlying disease, and in most cases will not constitute an AE. However, event(s) associated with the progression of disease should be recorded as an AE or SAE as applicable. The only time progression of disease should be considered an SAE is in case of a death for which the underlying events do not have corresponding terms associated with Grade 5 in the CTCAE V5.0. [†††]

17.6.5 Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. If a patient, including the female partners of a male study patient becomes pregnant during the study, the

[†††] From CTCAE V5.0: *Death due to disease progression that cannot be attributed to another CTCAE term associated with Grade 5.*

investigator or site personnel must notify the Medical Monitor within 5 working days after the investigator or site personnel become aware of the pregnancy. When a pregnancy has been confirmed in a subject (or a male subject's partner) during maternal or paternal exposure to study drug, within 6 months of the last dose of study drug or within 30 days after cessation of treatment if the subject initiates new anti-cancer therapy, the following procedures should be followed to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only)
- Consent must be obtained from female partners of male subjects
- The investigator must complete and submit the Pregnancy Notification Form to the sponsor or its designee within 24 hours of learning of the pregnancy
- A serum pregnancy test must be performed to confirm the urine pregnancy test result (female subjects only)

  If the serum test is negative and does not confirm the urine pregnancy test result, then:

  - The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine whether it is in the subject's best interest to resume study drug and continue participation in the study.
- The EOT visit evaluations must be performed (female subjects only)

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Pregnancy Notification Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on a Pregnancy Outcome Form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome. The baby should be evaluated for the first 8 weeks, or the duration specified in local regulations, whichever is later.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee following the instructions in Section 17.6.8.

17.6.6 Severity

The investigator must assess and categorize the severity of each AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 guidelines. The determination of severity for all other events not listed in the NCI CTCAE should

be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below in Table 18.[‡‡‡]

Table 18. NCI CTCAE Grading Scale

Grade	Clinical Characteristics
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention may be indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living
Garde 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life threatening, resulting in significant disability or incapacity, and/or representing the worst possible occurrence of that event with hospitalization probable
Grade 5	Death

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 17.6.1. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

17.6.7 Causality

Causality is a determination of whether there is a reasonable possibility that the investigational product or a study-related procedure is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. The relationship of each AE to administration procedures, paclitaxel, cisplatin/gemcitabine, durvalumab, and LSTA1 will be assessed separately by the investigator and the sponsor according to the following definitions:

Not related

- Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs

[‡‡‡] Common Terminology Criteria for Adverse Events. Version 5.0. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

- Is not related to the IP or study-related procedure (i.e., does not follow a reasonable temporal relationship to the administration of IP or study-related procedure or has a much more likely alternative etiology)
- No rationale exists for a relatedness

Unlikely related, and there is thought to be some remote possibility of a relatedness

- Has little or no temporal relationship to the IP or study-related procedure
- A more likely alternative etiology exists
- Some (perhaps weak) rationale exists for relatedness

Possibly related (both circumstances must be met)

- Follows a reasonable temporal relationship to the administration of IP or study-related procedure
- An alternative etiology is equally or less likely compared to the potential relationship to the IP or study-related procedure

Probably related (both circumstances must be met)

- Follows a strong temporal relationship to the administration of IP or study-related procedure
- Another etiology is unlikely or significantly less likely

Definitely related

- The evidence provides convincing proof of a relationship to the IP

17.6.8 Reporting for Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must enter the SAE in the EDC.

[redacted]

The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements. The sponsor may be required to report certain

SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor or delegate as soon as it becomes available.

[redacted]

A back-up paper report form will be provided as backup in the event EDC is inaccessible.

The investigator shall comply with local and national regulations and any applicable guidance (e.g., International Council on Harmonisation) for reporting any SAEs.

[redacted]

17.6.9 Reporting of an Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure (IB), unless otherwise specified in this protocol.

[redacted]

§§§ Auxiliary Medicinal Products in Clinical Trials. June 28, 2017. https://health.ec.europa.eu/system/files/2017-08/2017_06_28_recommendation_on_axmps_0.pdf

18. STATISTICS

18.1 Planned Statistical Analysis

Formal sample size calculations were not performed for this Phase 2a, placebo-controlled, proof-of-concept basket trial.

Cohorts may be analyzed separately for efficacy. Cohorts may also be analyzed separately for safety but will also be combined for an overall safety assessment.

Descriptive statistical methods will be used to summarize the efficacy, safety, and PK data from this study, with hypothesis testing performed for the primary and other selected efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum and maximum for continuous data and frequencies and percentages for categorical data.

Primary Efficacy Analysis: Kaplan-Meier survival curves will be constructed for each tumor cohort group by treatment group. Within each tumor group, LSTA1 median survival will be compared with that in the placebo group with log-rank tests. Cox regression analysis will be used to model the tumor groups and treatment groups simultaneously with tumor group, treatment group, and tumor-by-treatment group effects. Median survival will be estimated for each tumor-by-treatment group.

Secondary Efficacy Analyses:

- 3-, 6-, and 12-month survival rates, ORR and DCR will be compared, while controlling for tumor groups in a Fisher's test with a Wilson's confidence interval.
- Within each tumor group, LSTA1 median PFS and DOR will be compared with that in the placebo group with log-rank tests. Cox regression analysis will be used to model the tumor groups and treatment groups simultaneously with tumor group, treatment group, and tumor-by-treatment group effects. Median PFS and DOR will be estimated for each tumor-by-treatment group.

Efficacy analysis methods may include Kaplan-Meier survival analysis, analysis of covariance (ANCOVA), and Cox regression, mixed models, or logistic regression. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number.

The term 'treatment group' refers to all subjects in a specific tumor type basket arm dosing regimen.

There will be two (2) treatment groups per cohort in this study:

HNSCC

- LSTA1 3.2 mg/kg in combination with paclitaxel 175 mg/m^2 IV
- Matching LSTA1 placebo in combination with paclitaxel 175 mg/m^2 IV

1L Cholangiocarcinoma

- LSTA1 3.2 mg/kg in combination with cisplatin 25 mg/m^2 IV, gemcitabine 1000 mg/m^2 IV, and durvalumab 1500 mg IV
- Matching LSTA1 placebo in combination with cisplatin 25 mg/m^2 IV, gemcitabine 1000 mg/m^2 IV, and durvalumab 1500 mg IV

2L Cholangiocarcinoma

- LSTA1 3.2 mg/kg in combination with oxaliplatin 85 mg/m^2 IV, l-folinic acid 200 mg/m^2 **or** 400 mg/m^2 d,l-folinic acid IV, and fluorouracil (5-FU) 400 mg/m^2 (IV bolus) on day 1 followed by a continuous 46-hour infusion of 5-FU 2400 mg/m^2 repeated every 14 days
- Matching LSTA1 placebo in combination with oxaliplatin 85 mg/m^2 IV, l-folinic acid 200 mg/m^2 or 400 mg/m^2 d,l-folinic acid IV, and fluorouracil (5-FU) 400 mg/m^2 (IV bolus) on day 1 followed by a continuous 46-hour infusion of 5-FU 2400 mg/m^2 repeated every 14 days

Any statistical tests performed will be two-sided with an alpha level of 0.05. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

Safety Analysis:

All patients who receive any amount of study drug will be included in the final summaries and listings of safety data.

Frequencies of patients experiencing at least one AE will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Intensity (severity) of the AEs will be graded according to the CTCAE v5.0.

Summary tables will present the number of patients observed with AEs and corresponding percentages. The denominator used to calculate incidence percentages consists of patients receiving at least one dose of study drug. Within each table, the AEs will be categorized by MedDRA body system and preferred term. Additional subcategories will be based on event intensity and relationship to study drug.

Deaths and other SAEs will be tabulated.

Vital signs will be summarized using descriptive statistics.

Summary tables will be prepared to examine the distribution of laboratory measures over time.

Pharmacokinetic Analysis:

Concentration-time profiles will be constructed from the plasma samples obtained. Estimates of the AUC and slope of the terminal decay phase will be used to calculate values of the following PK parameters: apparent terminal phase half-life ($t_{1/2}$), total body clearance (CL), apparent time of maximum concentration (T_{max}), and apparent volume of distribution (Vd). Further details of the PK analysis will be provided in the statistical analysis plan.

Pharmacodynamic Analysis:

Pharmacodynamic analyses will be summarized using descriptive statistics, if applicable.

Subject Disposition, Demographic, and Baseline Characteristics

Subject disposition will be presented for all randomized subjects. For each treatment group the following will be presented: the number of subjects who meet all eligibility criteria, the number of subjects included in each analysis set, the number of subjects who completed the study and discontinued from the study, and the reasons for early discontinuation at any point. The number of subjects dosed will be presented and the number of days on study treatment will be summarized for all treated subjects. The number of dose interruptions, modifications, and discontinuations of all anti-cancer medication discontinuations will be summarized.

Demographic data and baseline characteristics including age, sex, race, and ethnicity, weight at Baseline, height at Baseline, and labs will be summarized using descriptive statistics for the Safety population and will be presented by treatment group. This information will be reviewed for baseline differences, but no statistical testing will be performed.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an AE that occurs during or after initiation of study drug. The number and percentage of subjects with TEAEs will be summarized by MedDRA System Organ Class and Preferred Term overall, by severity and by relationship to study drug or procedures.

18.2 Analysis populations

18.2.1 Safety analysis set

The safety analysis set will consist of all subjects who have been consented in the study and have received study drug.

18.2.2 Full Analysis Set (Efficacy analysis set)

This population will include all subjects who had a measurable lesion at baseline, received any amount of study drug, and completed a post treatment tumor assessment and/or discontinued due to documented clinical progression.

18.2.3 Per-protocol analysis set

The per-protocol analysis set will be a subset of the efficacy analysis set but will exclude subjects who had deviations that may impact critical efficacy variables. The per-protocol analysis set will be determined through blinded review of protocol deviations.

18.3 Efficacy Analysis

18.3.1 Definition of Measurable and Non-Measurable Lesions

Measurable Lesions at Baseline

The definition of a measurable lesion at baseline is dependent on the technical factors of the imaging studies that were used to evaluate the patient. The recommendations for the imaging parameters are based on the American College of Radiology (ACR) Practice Guidelines and Technical Standards. The ACR Practice Guidelines and Technical Standards define principles and technical parameters of radiologic and radiation oncology practice, which should generally produce desired health care outcomes. They describe a range of acceptable approaches for the diagnosis and/or treatment of disease for most patients, in most circumstances. Given differences in training, experience, and local conditions, the ACR Practice Guidelines and Technical Standards acknowledge the need for health care providers to exercise their independent medical judgment in making decisions regarding the use and specific details of any procedure.

For CT scanning of the chest, the ACR recommendation is that reconstructions should be less than 10 mm, and for CT of the abdomen and pelvis, the recommendation is the slice thickness should be 8 mm or less.

RECIST indicates CT images for chest, abdomen and pelvis should be performed using 5 mm reconstructions, but it is not explicitly stated as a requirement.

In preparing the technical specifications, we have followed the guidelines of the ACR, as 5 mm reconstructions are not the standard in the US or the rest of the world. Our proposal for modifying the size of measurable lesions at Baseline to two times the reconstruction interval of the Baseline/screening studies is consistent with the RECIST definition for a measurable lesion.

- Conventional CT should be performed with contiguous cuts of 10 mm or less in reconstruction interval. CT should be performed by use of a 5-8 mm contiguous reconstruction interval or less, where the neck and brain CTs should be done at 5 mm or less.

- Lesions that can be accurately measured in at least one dimension with the diameter being two times the reconstruction interval (RI) of the CT scan. Depending on the RI of the CT (5-8 mm or less recommended) measurable lesion size may be ≥ 10-16 mm. For example, a CT scan done at 8 mm RI would have a minimum lesion size of 16 mm in the longest dimension. The minimum size of a measurable lesion is 10 mm.

- Although initially identified as measurable lesion ≥10 mm, target lesions may in time reduce to <5 mm. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, if the target lesion is too faint to measure, the lesion measurement should be recorded as 5 mm if the lesion is still believed to be present. If the lesion has likely disappeared, the measurement should be recorded as 0 mm.

- In the instance where the reconstruction interval has changed from the Baseline to subsequent time points, it would be at the discretion of the radiologist whether this would affect interpretation. A note is made in the comment section of the source document, if applicable. The definition for target disease would not change and would be determined on the basis of the Baseline scan.

Non-Measurable Lesions

All other lesions that do not meet the criteria for measurable disease as described above as well as other truly non-measurable lesions (e.g., ascites, blastic bone lesions, pleural effusion, etc.), are considered non-measurable.

18.3.2 Definition of Target, Non-Target, and New Lesions (RECIST guidelines)

Target Lesions

Up to five target lesions, a maximum of two per organ, will be chosen for measurement over the course of the study. The distribution of these target lesions should be representative of the subject's overall disease. Target lesions should not be chosen from a previously irradiated area unless lesions in those areas have documented progression.

Target lesions must be measurable at Baseline. These lesions will generally be the largest lesions, most reliably measured, and most representative of the patient's sites of disease.

For any target lesion at any time point, measurements will be taken and recorded uni-dimensionally. The longest diameter of each tumor lesion or the short axis of each lymph node will be measured and recorded. The sum of the diameters for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the target lesions. For the consideration of progressive disease, the nadir of the sum diameters for the target lesions will be used as reference.

The following conventions will be applied in selecting target lesions in patients who have received prior radiation therapy:

- Intrathoracic measurable lesions in the periphery of the lung, just deep to the radiated chest wall concordant with the radiation portal ***cannot*** be selected as target lesions. However, if the lesions are more centrally located in the chest and do not appear in regions showing evidence of radiation injury (e.g., scarring, radiation pneumonitis, etc.), they can be selected as target lesions. *The assigned radiologist will document descriptions of radiation damage in the comments field.*

- Prior bone radiation (e.g., vertebral, rib, pelvis, femur, etc., as stated on the Prior Radiation Therapy Form) would ***not*** preclude the selection of measurable lesions in adjacent structures unless signs of radiation injury are evident (e.g., scarring).

- Prior soft tissue radiation (e.g., supraclavicular radiation, radiation of internal mammary lymph nodes, etc., as recorded on the Prior Radiation Therapy Form) would preclude the selection of measurable disease in the site of radiation unless the site confirms that the lesions are new since radiation was completed.

Non-Target Lesions

All of the sites of disease present at Baseline not classified as target lesions will be classified as non-target lesions. Non-target lesions must be qualitatively assessed at each subsequent time point. Examples of non-target lesions include:

- Blastic bone lesions
- Leptomeningeal disease
- Lymphangitis of the skin or lung
- Irradiated lesions that have not shown progression
- Measurable lesions beyond the maximum number of 5
- Groups of lesions that are small and numerous
- Pleural effusion/pericardial effusion/ascites

New Lesions

Unequivocal new lesions are those that were not present at Baseline. At each time point, the presence of new lesions will be determined. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Lesions that are encountered (subsequent to the Baseline) in anatomic locations that were not scanned at Baseline will be considered new lesions and will represent progressive disease.

19. DATA HANDLING AND RECORD KEEPING

19.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement and with national, local, and institution-specific patient privacy regulations.

19.2 Data Management

[redacted]

An Electronic Data Capture (EDC) system will be used for data collection and query handling. The system will have been validated and will be compliant with Food and Drug Administration (FDA), ICH, and European Union (EU) regulations and guidelines. No data will be requested other than what is routinely entered in the eCRFs.

The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided. The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

19.3 Source Data/Documents

The investigator will maintain complete and accurate study documentation in a separate file. Documentation may include medical records, records detailing the progress of the study for each subject, signed informed consent forms, drug disposition records, correspondence with the IRB and the study monitor/Sponsor, enrollment and screening information, data worksheets, SAE laboratory reports (if applicable), data clarifications requested by the Sponsor, etc.

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the Sponsor or Sponsor's representatives, review by the IRB, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the Sponsor of contact, cooperate with the authority, provide the Sponsor with copies of all documents received from the authority, and allow the Sponsor to comment on any responses, as described in the Clinical Study Agreement.

Questions or interpretations of the protocol will be referred to the Sponsor. The Sponsor is responsible for providing interpretation of all data questions.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data reported in the eCRF derived from source documents should be consistent with the source documents.

The investigator is responsible for the procurement of data and for the quality of data. Only designated study site personnel shall record or change data.

The investigator will comply with the procedures for data recording and reporting. Any corrections to study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry and include the reason for change, if not obvious. The use of correction fluid and erasing are prohibited.

The primary source document for this study will be the subject's medical record. If the investigator(s) maintains separate research records, both the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Data recorded on source documents will be entered into eCRFs. The investigator must promptly review the completed eCRFs for each subject. A study monitor representing the sponsor will review the source documents against the eCRF on a regular basis throughout the study.

The PI at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between Lisata and the PI must be in place before any study-related procedures can take place, or subjects are enrolled.

19.3.1 Archiving of Study Documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

19.4 Data Security

In the event of any unauthorized breach or suspected breach, the following mitigations will be implemented by the Sponsor and/or applicable vendors:

- Containment: Isolate the affected systems in order to limit access to sensitive information.
- Notification: Notify the appropriate parties about the breach. Notification should be timely and transparent, providing accurate information about the breach and its potential impact.

- Investigation: Investigate to determine the root cause and extent of the breach. This may involve analyzing system logs, interviewing employees, and reviewing security policies and procedures.

- Remediation: Address the vulnerabilities that led to the breach. This may involve updating security policies, implementing additional security controls, or patching software vulnerabilities.

- Communication: Communicate in a clear and timely manner with all stakeholders. This includes information about the status of the investigation and the steps being taken to address the breach.

- Monitoring: Implement ongoing monitoring and analysis to detect any further security incidents. This may involve implementing intrusion detection and prevention systems, conducting regular vulnerability assessments, and performing penetration testing.

20. QUALITY CONTROL AND QUALITY ASSURANCE

20.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by an Institutional Review Board [IRB]), International Council on Harmonization (ICH), Good Clinical Practice (GCP), and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term "investigator" as used in this protocol and in study documents refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

20.2 Training

Before the first subject is entered into the study, a Lisata representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and train them in any study-specific procedures and system(s) utilized.

The Principal Investigator (PI) will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

20.3 Auditing

The Sponsor and/or Sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

20.4 Non-Compliance with the Protocol

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of study monitor, change of phone number). In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the Sponsor immediately by phone and confirm notification to the Sponsor in writing as soon as possible, but within 5 working days after the change is implemented. The investigator will also notify the IRB of the emergency change.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the Sponsor may terminate the investigator's participation. The Sponsor will notify the IRB and applicable regulatory authorities of any investigator termination.

21. ETHICAL AND REGULATORY REQUIREMENTS

21.1 Ethical Conduct of the Study

This study will be conducted in accordance with this protocol, the International Council on Harmonisation Guideline for Good Clinical Practice E6(R2) (09 November 2016) and all applicable national and local regulatory requirements.

21.2 Participating Centers

Participating clinical sites must have an appropriate IRB governance since they are actively engaged in research and provide informed consent. Health Insurance Portability and Accountability Act (HIPAA) and applicable local regulations will be followed by each participating institution in accordance with each institution's requirements. The participating sites will obtain approval from their corresponding review boards in accordance with their local procedures and institutional requirements.

The investigator is required to keep accurate records to ensure the conduct of the study is fully documented.

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants participating in this study. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (obscuring

any personally identifying information). Authorized representatives, as noted above, are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals. The investigational site will normally be notified in advance of auditing visits.

21.3 Informed Consent and Protected Health Information

Written informed consent must be obtained from each patient (or the patient's legal representative) prior to performing any study-specific Screening Period evaluations.

The proposed informed consent form must be in compliance with regulatory regulations and must have been reviewed and approved by the Sponsor and the Investigator's IRB or Independent Ethics Committee (IEC) prior to submission to the reviewing IRB/IEC. The proposed informed consent form should contain the 20 elements of informed consent described in ICH E6 4.8, including a full explanation of the purpose and nature of the study, a description of the procedures, the possible advantages, risks, alternate treatment options, and a statement of confidentiality of patient study records, a statement regarding voluntary compensation and availability of treatment in the case of injury, an explanation of whom to contact about the research, the patient's rights, and notification that participation is voluntary and refusal will involve no penalty or loss of medical benefits. The consent should also indicate by signature that the patient, or where appropriate, legal guardian/representative, permits access to relevant medical records by the Sponsors staff, the Sponsors duly appointed representatives, and by representatives of applicable regulatory agencies. Additionally, Investigators in regions with specific regulations regarding patient's rights have a responsibility to follow and document their fulfillment of those regulations.

The Investigator will be responsible for obtaining written informed consent from potential patients or the patient's legally authorized representative prior to any study specific screening and entry into the study. A copy of the signed document will be provided to the patient, and a copy will be maintained with the patient's records. The original will be retained by the Investigator. The source documents for each individual shall document that the informed consent was obtained prior to participation in the study.

The Sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure and study procedures. The informed consent will be updated, if necessary. This new information and/or revised informed consent form that has been approved by the applicable IRB, will be provided by the investigator to the subjects who consented to participate in the study and are still actively participating.

21.4 Risks and Benefits

The risks of this study are presented in the Investigator's Brochure and the informed consent form. There is no guaranteed benefit to subjects for their participation in the study.

21.5 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided to the patients will be reviewed and approved/given favorable opinion by an IRB. The Investigator's Brochure will be provided for review. The IRB's composition or a statement that the IRB's composition meets applicable regulatory criteria will be documented. The study will commence only upon the Sponsor's receipt of written approval/favorable opinion from the IRB, as described in the Clinical Study Agreement.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the IRB. The protocol amendment will only be implemented upon the Sponsor's receipt of approval and, if required, upon the Sponsor's notification of applicable regulatory authority approval.

Lisata or delegate should approve any modifications to the ICF that are needed to meet local requirements.

Lisata will provide Regulatory Authorities, IRB/IEC, and PIs with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

22. STUDY ADMINISTRATION

22.1 Monitoring

During the study, a CRA will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts).

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

The CRA will be available between visits if the investigator(s) or other staff at the center needs information or advice about the study conduct.

22.2 Medical Monitor Coverage

Each subject will be provided with contact information for the PI and the site coordinator(s). In an emergent situation, a subject may present to a medical facility where the treating health care provider is not involved with this clinical trial. The treating healthcare provider may require additional information on the study drug, and the subject should provide contact information for the site coordinator(s) or the PI.

The PI will then be required to update the medical monitor.

All adverse events will be recorded on the adverse event forms, and the treatment related SAEs will be sent to the IRB, per their reporting requirements, and to the Sponsor. The study medical monitor or designee will review all SAE reports. Further details are captured in the study medical monitoring plan.

22.3 Laboratory Accreditation

Any laboratory facility to be used for analysis of routine clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation. Licensure/accreditations and reference values and/or normal ranges for the test results must be provided to the Sponsor or designee.

The sponsor or designee must be notified immediately in writing of any changes occurring in reference values during the study.

22.4 Financing and Insurance

The investigator will comply with investigator financing, investigator/Sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

22.5 Publication Policy

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

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